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AMERICAN COLLEGE CHEST PHYSICIANS

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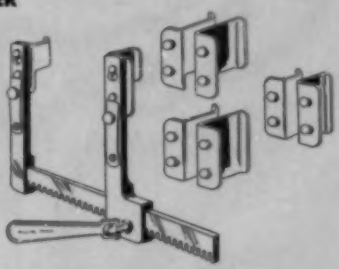

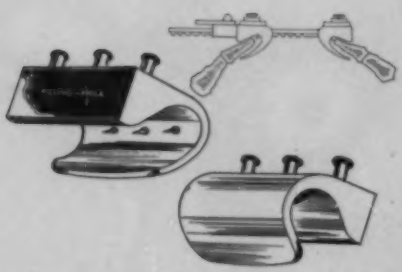

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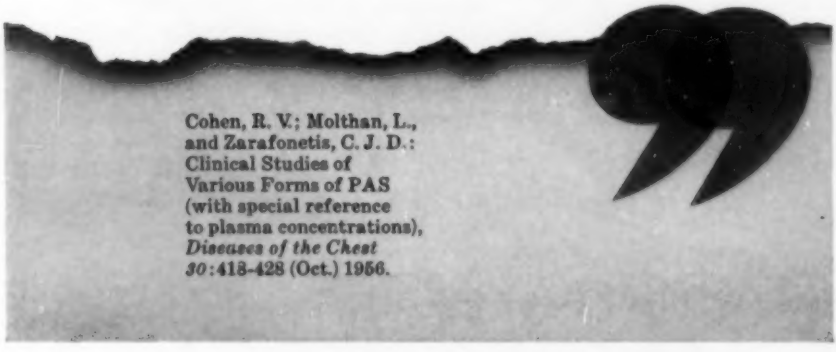

Cohen, R. V.; Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations), *Diseases of the Chest* *30*:418-428 (Oct.) 1956.

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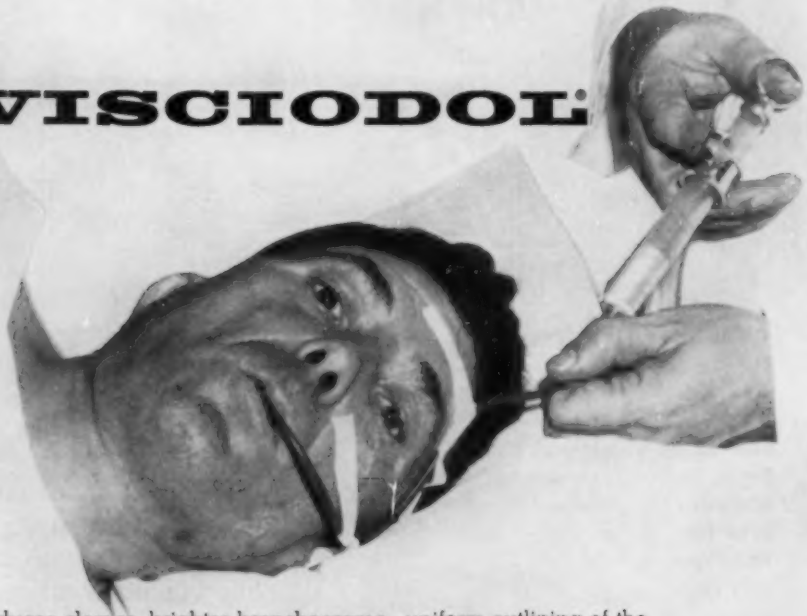

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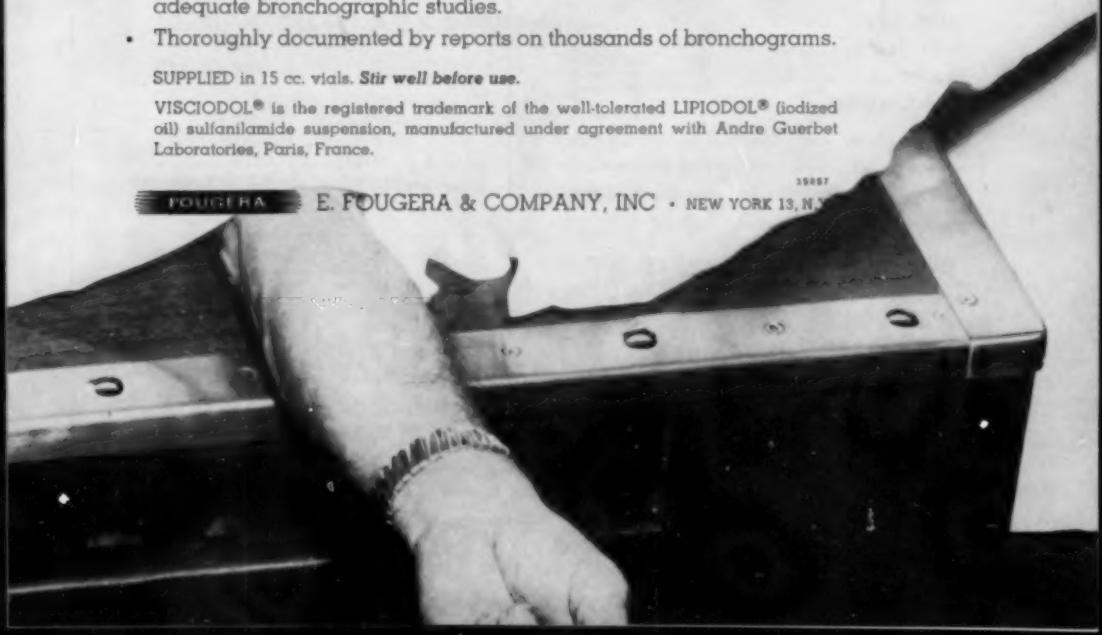

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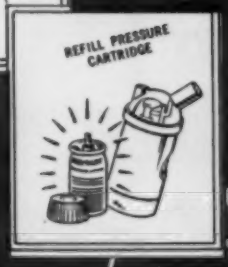

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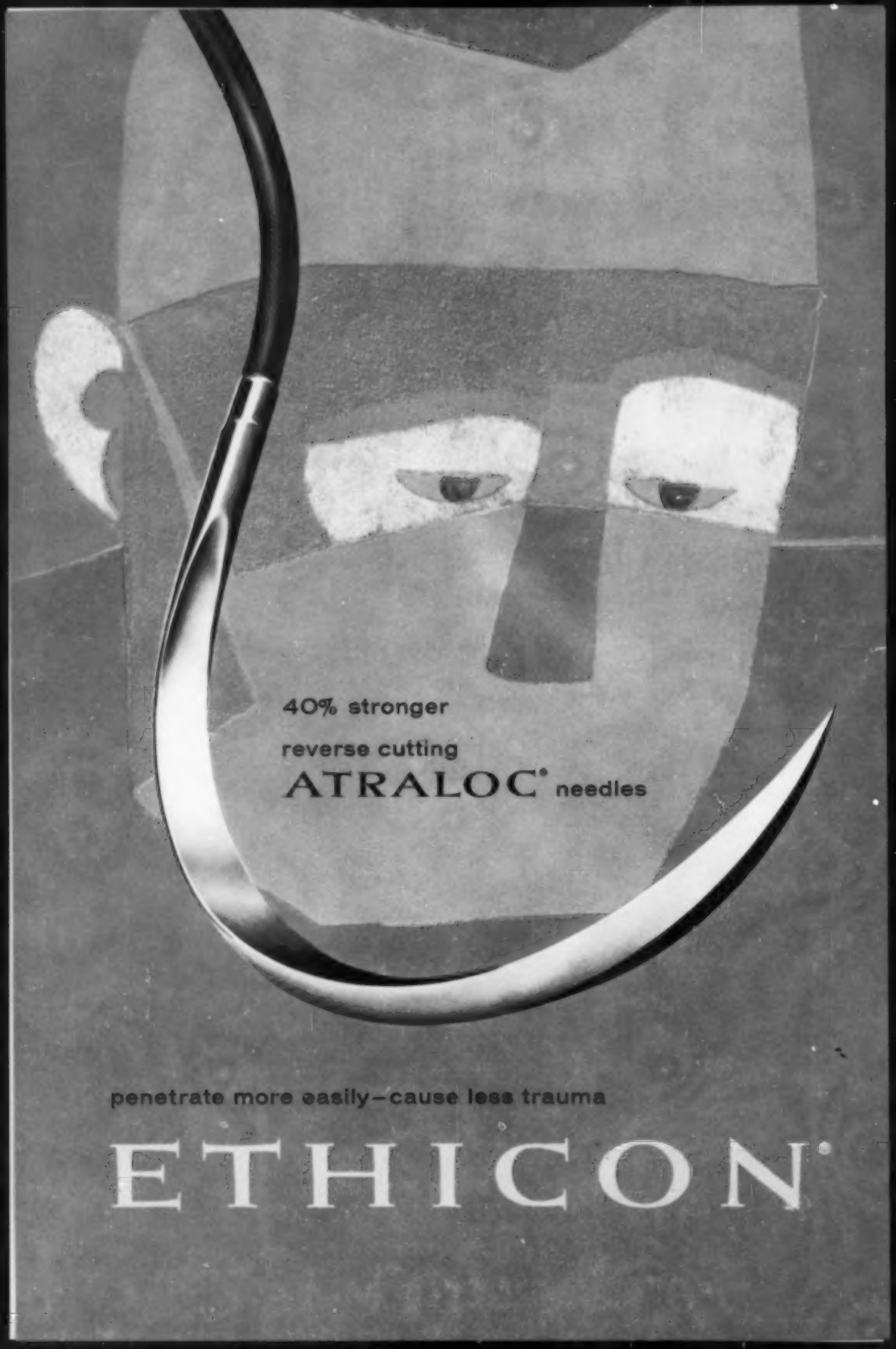
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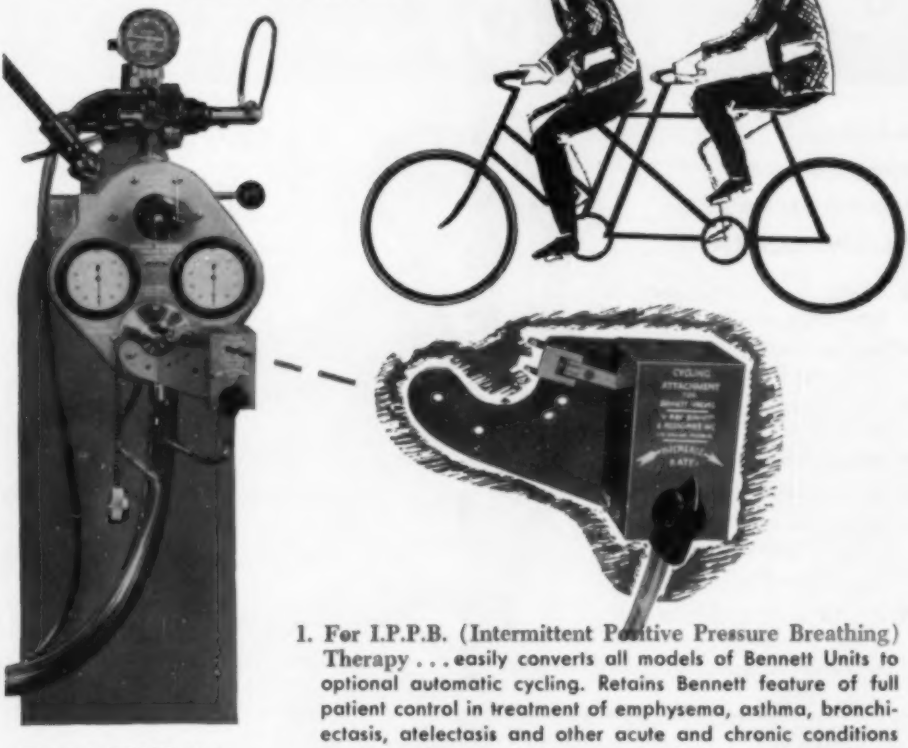

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DISEASES of the CHEST

VOLUME XXXII DECEMBER, 1957 NUMBER 6

Experiences with the Therapy of Sixty Cases of Deep Mycotic Infections*

PATRICK H. LEHAN, M.D.,** J. LEWIS YATES, M.D., F.C.C.P.,***
CHARLES A. BRASHER, M.D., F.C.C.P.,† HOWARD W. LARSH, Ph.D.‡
and MICHAEL L. FURCOLOW, M.D., F.C.C.P.§
Kansas City, Kansas

A host of chemotherapeutic agents and antibiotics have been employed in the treatment of deep mycotic infections. With the exception of actinomycosis and nocardiosis the commonly employed antimicrobial agents have proved to be ineffective. In the past few years a number of new antifungal agents have received attention as possible therapeutic drugs. Since the literature is not clear on the efficacy of these drugs, we would like to briefly review the subject and add our experiences with these agents. Recently we have extended pre-existing clinical trials[1] to include a newly described antibiotic, amphotericin B. Preliminary results with this agent in the treatment of histoplasmosis and cryptococcosis are quite promising and will be presented in detail.

Antecedent Therapeutic Trials

Aromatic Diamines: Elson[2] in 1945 reported that certain of the diamines exerted a fungistatic effect on *Blastomyces dermatitidis in vitro.* Following this a series of reports[3-6] appeared in the literature indicating favorable results obtained with stilbamidine and later 2-hydroxystilbamidine in the treatment of blastomycosis. Of the five cases of systemic blastomycosis treated by our group results have likewise been favorable. All of our cases received 2-hydroxy 4,4′ stilbenedicarboxamide (2-hydroxystilbamidine, Merrell) intravenously in a daily dose of 225 mg. In three cases complete clearing occurred after a 30 day course of therapy. The remaining two patients required a second course before complete recovery.

Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

*From the Department of Health, Education, and Welfare, Public Health Service, Bureau of State Services, Communicable Disease Center, and the Missouri State Sanatorium, Mount Vernon, Missouri.

** ‡ § Sr. Asst. Surgeon (R), Mycology Consultant, and Medical Director, respectively, Kansas City Field Station, PHS, University of Kansas Medical Center, Kansas City, Kansas.

*** †Chief of Internal Medicine and Medical Superintendent, respectively, Missouri State Sanatorium.

In view of the remissions produced in blastomycosis, two cases of chronic progressive cavitary histoplasmosis and one with disseminated disease were treated with a similar therapeutic regime without demonstrable effect. *In vitro* studies[7] indicate that the body fluid levels required to inhibit the growth of *Histoplasma capsulatum* far exceed those which can be obtained.

With the development and availability of the analog, 2 amino 4,4′ stilbenedicarboximide (aminostilbamidine, Merrell) three patients with cavitary histoplasmosis were treated with 250 mg. intravenously daily for 30 to 60 days. No definite therapeutic effect could be demonstrated.

MRD-112: In 1949 Tilford et al.[8] described the properties of B diethylaminoethyl fencolate (MRD-112, Merrell). Several years later Ludwig et al[9] described its antifungal potentialities. Michael and Vogel[10] reported the first case of disseminated histoplasmosis treated successfully with this agent. Shortly after this publication the patient reportedly relapsed. Recently the "beneficial effect" of MRD-112 on the course of cavitary histoplasmosis has been reported.[11] At the time of surgical resection, however, *H. capsulatum* was recovered from the pulmonary lesion. We have undertaken clinical trials with this agent in a total of 14 patients. Of these, two had cryptococcal meningitis, two disseminated histoplasmosis

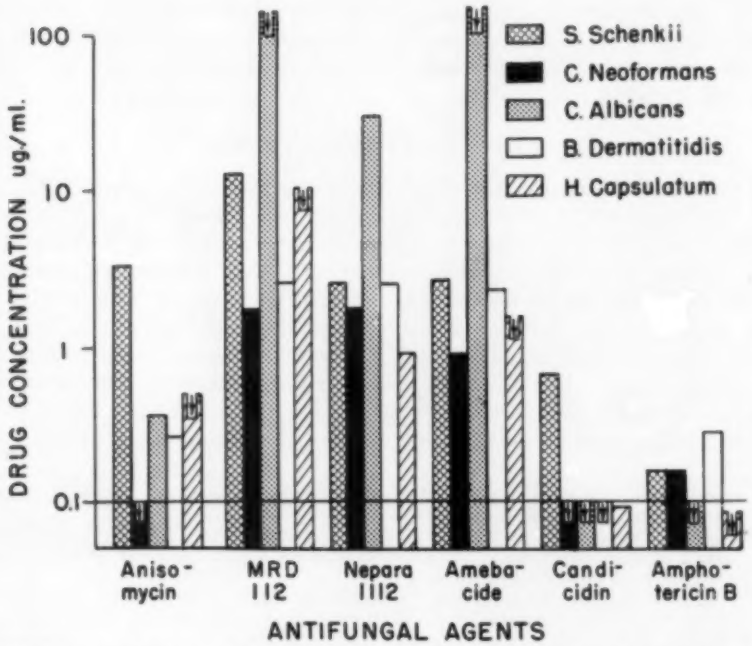

FIGURE 1: Comparison of the concentrations of six antifungal agents necessary to produce 50 per cent inhibition of the yeast phase of pathogenic fungi recently isolated from clinical cases.

and 10 cavitary histoplasmosis. All received daily intravenous doses from 150 to 250 mg. for periods of 30 to 60 days. The administration of MRD-112 did not alter the course or fatal outcome in either cryptococcal meningitis or disseminated histoplasmosis. Similarly, no effect was demonstrated among those with cavitary histoplasmosis. Six of the latter cases subsequently had surgical resection of their lesions[12] and in all instances *H. capsulatum* was recovered from the lesions.

Ethyl Vanillate: Christie and colleagues[13] in 1951 reported favorable results with ethyl vanillate in the treatment of disseminated histoplasmosis. Since that time a number of favorable results and failures have been reported[14-16] in the literature. Although we have had no experience with this drug, the apparently erratic results obtained by others and the narrow therapeutic index led us to search for a better therapeutic agent.

Nystatin: In 1951 Hazen and Brown[17] described an antifungal agent derived from several species of *Streptomyces*. This antibiotic was first called "fungicidin" but subsequently renamed nystatin (Mycostatin, Squibb). Animal studies by Campbell[18] revealed that nystatin was an effective *in vivo* antifungal agent. Negligible absorption from the gastrointestinal tract precluded the use of oral nystatin in the treatment of the deep mycotic infections. Trials with an intravenous preparation were undertaken in four patients with cavitary histoplasmosis and one with cavitary coccidioidomycosis. In four of these marked side reactions consisting of chills, fever, nausea and vomiting prevented a full course of therapy. One case with cavitary histoplasmosis received 200,000 units daily for 62 days without demonstrable therapeutic or toxic effect.

Amebacide: In 1952 the Eli Lilly Co. called our attention to a chemical compound 1, 2 Bis para (n-hexyl methylaminomethyl) phenoxy ethane dihydrochloride (amebacide CT 686). *In vitro* studies[19] revealed this to have considerable activity against a variety of fungi. Since this compound was relatively soluble in water, therapeutic trials with an oral preparation were undertaken. Fourteen cases of cavitary histoplasmosis received oral doses ranging from 45 to 300 mg. daily for a period of three months. Results were disappointing; in only one instance was it thought that the drug exhibited some beneficial effect on the patient's clinical course.

Therapeutic Trials with Amphotericin B

Recently members of the Squibb Institute of Medical Research have isolated and described a new antifungal antibiotic derived from a soil *Streptomyces*.[20, 21] Studies by this group indicate that amphotericin B is a weak base and is amphoteric as demonstrated by its greater solubility in acidic or basic aqueous alcoholic solvents. While the exact chemical structure of this compound is not known its molecular formula has been established as C_{46} H_{73} NO_{20}.[22] Ultraviolet absorption maxima indicate that there is a conjugated haxaenic or heptaenic system in amphotericin B.

In vitro studies by Gold, Stout, Pagano and Donovick[20] reveal that amphotericin B does not have antibacterial activity but is effective in inhibiting the growth of the yeast and yeastlike fungi. Recent *in vitro* stud-

ies[23] in this laboratory with five strains of yeast phase *H. capsulatum* have shown that less than 0.1 mcg./ml. of amphotericin B was needed to produce 50 per cent inhibition of all strains. Figure 1 compares the relative activity of amphotericin B with that of other antifungal agents under investigation against a variety of pathogenic fungi. It should be noted that only candicidin compared favorably to amphotericin B. The toxicity of candicidin has prevented clinical evaluation. Steinberg et al.[24] and Louria[25] have shown in mice that amphotericin B is an effective *in vivo* antifungal agent with a high therapeutic index.

Cryptococcosis: All the cases in this series presented clinical evidence of meningitis and *Cryptococcus neoformans* was readily recovered from the spinal fluid. In each instance pathogenicity was confirmed by intracerebral mouse inoculation. Table I outlines the pre-treatment status and cultures, the therapeutic regime and response of these patients. It should be noted that both patients who failed to improve were *in extremis* and expired shortly after instituting therapy. Although Case 2 received oral therapy only, she improved and has been symptom free for one year. It is possible that she was undergoing spontaneous remission when therapy was started. In each instance where intravenous therapy was employed the patients were followed with spinal fluid cultures performed at weekly intervals. Despite repeated cultures, in no instance was the organism recovered after two weeks or more of intravenous therapy. Case 4 had, in addition to meningitis, several cutaneous lesions of three months duration due to *C. neoformans*. Figure 2 presents the rather dramatic healing of one of these lesions while under therapy.

In all but one case the cerebrospinal fluid cell count, sugar and protein have reverted to normal. In the exception (Case 5) gradual but progressive reduction in cell counts and protein was noted but without completely re-

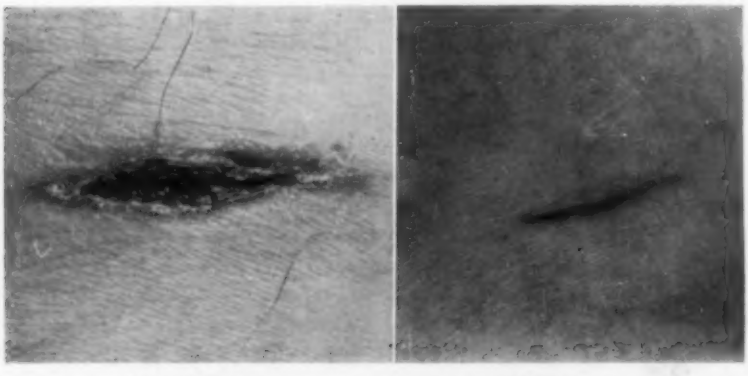

FIGURE 2A FIGURE 2B

Figure 2A (Case 4): Chronic cutaneous lesion overlying the 11th rib posteriorly as it appeared the day therapy was instituted. Present without change for 3 months. *C. neoformans* recovered from lesion.—*Figure 2B* (Case 4): Same lesion as it appeared approximately 2 weeks after instituting intravenous amphotericin B therapy. No evidence of recurrence after 4 months.

TABLE I

CRYPTOCOCCAL MENINGITIS

Summary of Clinical and Laboratory Data on Cases Treated with Amphotericin B

	Pre-Treatment			Therapeutic Regime			Post Treatment		
Case	Clinical Condition	Cultures		Route	Dose/ Frequency	No. Doses	Clinical Response	Cultures	Comments
1. J. D. 56 W. M.	Moribund	Spinal Fluid Gastric Urine	+ + +	Oral	2 gm./q.d.	4	Expired	Positive	Post-mortem denied
2. H. M. 50 W. F.	Good	Spinal Fluid	+	Oral	2 gm./q.d.	30	Good	Negative	Improving prior to therapy Asymptomatic 1 year
3. L. O. 63 W. M.	Moribund	Spinal Fluid	+	Intravenous	50 mg./q.d.	7	Expired	Positive	Diabetic—5 years Post-mortem cultures Positive
4. E. S. 37 W. M.	Poor	Spinal Fluid Skin	+ +	Intravenous	50 mg./q.d. 80 mg./q.d. 100 mg./q.o.d.	4 9 4	Good	Negative Negative	Concomitant Lymphoma Skin lesions healed Asymptomatic—5 months
5. H. D. 62 W. M.	Poor	Spinal Fluid	+	Intravenous	100 mg./q.d. 50 mg./q.d. 50 mg./q.o.d.	8 4 10	Fair	Negative	Well—5 months CSF Protein remains elevated
6. R. M. 31 W. F.	Fair	Spinal Fluid	+	Intravenous	50 mg./q.d. 100 mg./q.o.d.	13 27	Good	Negative	Asymptomatic 4 months Spinal fluid normal

turning to normal during the short period of follow up. Case 6 is presented here briefly to illustrate the response noted.

*Case 6:** This 31 year old white woman was admitted to the hospital for the fourth time on December 27, 1956 with the chief complaint of severe headaches. She dated the onset of illness to May 1956 when she noted the sudden onset of severe generalized headaches, stiff neck and low grade fever. In the succeeding four months she was hospitalized on three occasions for persistence of these symptoms. In August 1956, she noted the onset of a constant "roaring" sensation in both ears and brief episodes of visual and auditory hallucinations. At this time it was observed that there was some "blurring" of the optic discs and the cerebrospinal fluid pressure was found to be consistently about 400 ml. of water. Ventriculograms at this time were interpreted as normal. Because of the unremitting headaches and frequent episodes of vomiting, spinal tap was performed every week to reduce the cerebrospinal fluid pressure. Despite the frequent spinal taps severe headaches as well as low grade temperature persisted. Approximately one month prior to admission she began having transitory attacks during which time she would develop numbness of the lower half of her face and the buccal mucosa on the right side. These attacks were associated with considerable difficulty in speaking intelligibly.

Physical examination on this admission was essentially negative except for bilateral "blurring" of the optic discs and questionable left facial weakness. She was seen by an ophthalmologist who felt that this blurring did not represent papilledema.

A spinal tap performed the day after admission revealed an opening pressure of 280 ml. of water. On examination, the fluid was found to contain 120 white blood cells per mm.^{3} (98 per cent lymphocytes), 29 mg. per cent sugar and 144 mg. per cent total protein. Routine bacterial cultures and cultures for *Mycobacterium tuberculosis* were negative. Cultures for fungi were positive for *C. neoformans*. Hematopoietic, renal and hepatic studies and chest roentgenogram were considered within normal limits.

On January 7, 1957 she was started on intravenous amphotericin B., 50 mg. daily, which was administered for 13 days. This was followed by 100 mg. every other day for an additional 27 doses. On the 10th day of therapy, a spinal tap revealed the following: opening pressure 250 ml. of water, 29 white blood cells (100 per cent lymphocytes), sugar 47 mg. per cent and total protein 70 mg. per cent. Cultures and intracerebral inoculation of spinal fluid were negative for *C. neoformans* and remained so in nine succeeding spinal taps over the next five months. Following the initial drop in cerebrospinal fluid protein and cells and the rise in sugar only minor changes were noted over the next two months. Three weeks after the completion of intravenous therapy the cerebrospinal fluid pressure, cell counts, protein and sugar were all within normal limits.

After one week of therapy she was essentially afebrile and asymptomatic except for occasional headaches. By the third week the headaches had almost completely disappeared. Five months after instituting therapy she was asymptomatic.

Histoplasmosis: As a result of our interest in this disease and our geographical location suitable cases with this entity were most readily available for therapeutic trials. In an effort to critically interpret our results in the treatment of histoplasmosis we will consider separately the three forms of the disease we have treated. All cases selected for trials were proved by isolation of the fungus by culture. Division of cases into the various classifications is based on criteria previously outlined by Furcolow.[26]

1) *Progressive Disseminated Histoplasmosis:* Six cases with this almost universally fatal entity received amphotericin B. The first two received only oral drug and in both instances temporary clinical improvement and negative cultures were obtained while under active therapy. Both patients relapsed approximately one month after the therapy was stopped. The remaining four received intravenous therapy as outlined in Table II. While two of them expired, only three doses were administered before their de-

*Case included with permission of Dr. Martin FitzPatrick, of the University of Kansas Medical Center, who will report the case in detail.

TABLE II
DISSEMINATED HISTOPLASMOSIS
Summary of Clinical and Laboratory Data on Cases Treated with Amphotericin B

	Pre-Treatment			Therapeutic Regime			Post-Treatment		
Case	Clinical Condition	Cultures		Route	Dose/ Frequency	No. Days Treated	Clinical Response	Cultures	Comments
7. S. A. 4 W. F.	Fair	Bone Marrow Lymph Node	— +	Oral	1 gm./q.d. 2.4 gm./q.d.	90 120	Temporary Improvement Questionable	Negative Negative	Relapse after discontinuation of therapy. Has persistent hepatosplenomegaly
8. D. R. 50 W. M.	Poor	Bone Marrow Sputum Laryngeal Lesion	+ + +	Oral	2 gm./q.d. 4 gm./q.d.	60 73	Temporary Improvement Expired	Negative Not Done	1 Week after discontinuing therapy cultures again positive. Rec'd. cortisone for adrenal insufficiency Suddenly expired—2 months after therapy
9. M. H. 5 mo. C. F.	Moribund	Bone Marrow	+	Intravenous	5 mg./q.d.	3	Expired	.....	Post-mortem cultures Positive
10. E. H. 69 W. M.	Moribund	Sputum	+	Intravenous	50 mg./q.d.	2	Expired	.....	Post-mortem Denied
11. J. A. 69 W. M.	Moribund	Sputum Bone Marrow	+ +	Intravenous	100 mg./q.d. 50 mg./q.d. 50 mg./q.o.d. oral 2 gm./q.d.	6 15 34	Good	Negative	Asymptomatic 6 months Rec'd. oral therapy 2 additional months
12. F. Y. 56 W. M.	Poor	Oral Ulcer	+	Intravenous	50 mg./q.d. 100 mg./q.o.d.	23 17	Good	Negative	Complete healing oral lesion—20 lb. weight gain —Asymptomatic 4 months

mise. The remaining cases demonstrated rather dramatic clinical improvement and cultural conversion. Case 12 had no demonstrable pulmonary lesions at the time the diagnosis was made. He did, however, have a granulomatous ulcerating lesion on the floor of the mouth shown to be due to *H. capsulatum*. Figure 3 depicts this lesion prior to and three weeks after therapy was instituted. Case 11 will be briefly presented here as an illustrative response of this type of disease to amphotericin B.

*Case 11:** This 69 year old white man first sought the aid of his physician in May 1956 complaining of gradual weight loss, anorexia, weakness and low grade temperature over the preceding five months. During the following two months his symptoms increased to the point where he required hospitalization. Findings on physical examination at this time were essentially negative except for palpable liver and spleen. Pathologic examination of liver sections obtained by needle biopsy were interpreted as "chronic granuloma consistent with Boeck's Sarcoid." A roentgenogram of the chest revealed moderate pulmonary emphysema with increased hilar markings and multiple soft parenchymal shadows particularly on the left (Figure 4A). At this time a tentative diagnosis of sarcoidosis was made and he was started on prednisone.

During the following month he remained afebrile and appeared to improve clinically. Shortly thereafter fever returned and he began a rapid downhill course. On September 17, 1956, he was readmitted to the hospital in a moribund state. Physical examination at this time revealed a chronically ill, febrile, disorientated elderly man with hepatosplenomegaly. A roentgenogram of the chest showed a questionable increase in pulmonary infiltrations. Cultures of the bone marrow and sputum yielded *H. capsulatum*.

A two months course of intravenous amphotericin B supplemented with oral drug, as outlined in Table II, was started on September 19, 1956. Ten days after instituting therapy, cultures for *H. capsulatum* were found to be negative as have all subsequent cultures. A chest roentgenogram one month later demonstrated "marked clearing" (Figure 4B). During this period he became afebrile, and in succeeding months the hepatosplenomegaly slowly regressed although the tip of the spleen remains palpable. He has remained afebrile and continues to be well after eight months.

*Case included with permission of Dr. Marion J. Greve, of Dallas, Texas, who will report the case in detail.

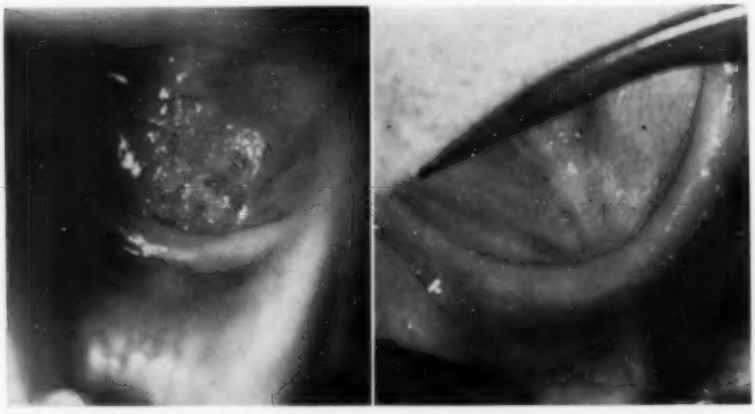

FIGURE 3A FIGURE 3B

Figure 3A (Case 12): Ulcerating granulomatous lesion involving the major portion of the floor of the mouth. Culture and biopsy revealed *H. capsulatum*. Ulcerative disease has destroyed both sublingual caruncles.—*Figure 3B* (Case 12): Complete healing of lesion after three weeks of intravenous amphotericin B. A small fistulous tract through which both submaxillary ducts empty can be seen to the right of the attachment of the frenulum.

2) *Chronic Progressive Pulmonary Histoplasmosis:* Six patients who were classified in this category were selected for therapeutic trials with oral and intravenous amphotericin B. Of these, five had cavitary disease and the remaining case had long standing apical disease without cavitation. Only cases in which *H. capsulatum* has been repeatedly isolated from the sputum were selected for study. In an effort to minimize the possible effect of bed rest and general supportive measures all cases were observed for two to three months before therapy was instituted. Only one (Case 17) had significant clinical and x-ray film improvement on bed rest alone. Drug therapy was withheld in this case until his clinical status and x-ray films were stable.

The problems of evaluation of therapy on a short term basis for this type of disease are comparable to those with advanced pulmonary tuberculosis. The criteria used in evaluating response to therapy were: (1) Changes in clinical status, (2) X-ray changes, (3) Complement fixation titer changes, (4) Conversion of sputum cultures. A summary of the clinical and laboratory data on these patients is presented in Table III. It should be noted that cases 13 and 14 received largely prolonged oral therapy. Both of these cases showed clinical improvement and slight to moderate x-ray film change but sterilization of the sputum was obtained in case 13 only. The remaining four cases received oral drug supplemented by significant amounts of intravenous amphotericin B. In all these cases clinical and x-ray improvement as well as sterilization of the sputa was accomplished. In only one instance, however, was cavity closure noted. Figure 5 demonstrates the typical pulmonary lesions and their response to amphotericin B. Case 15 is presented in detail to point out the similarity of this entity to tuberculosis and its response to therapy.

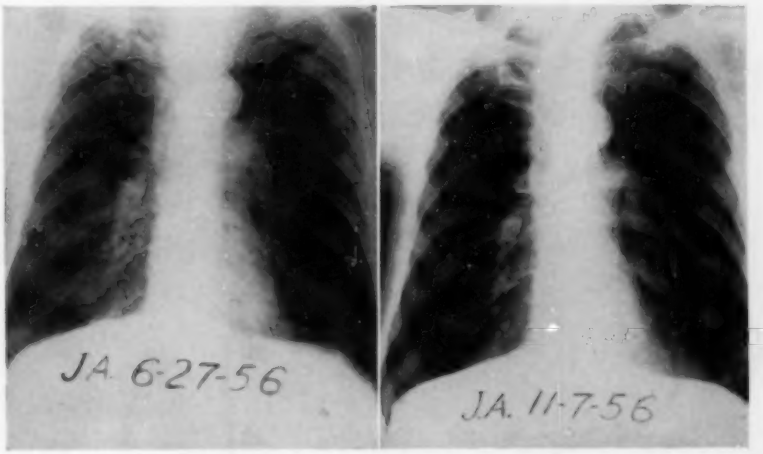

FIGURE 4A FIGURE 4B

Figure 4A (Case 11): Disseminated histoplasmosis. Chest roentgenogram as it appeared prior to therapy.—*Figure 4B* (Case 11): Marked clearing of pulmonary infiltrates after approximately 2 months therapy with intravenous amphotericin B.

Case 15: This 37 year old white man accountant had been well until the spring of 1956 when he experienced an influenza-like illness. Following this, recurrent low grade fever, night sweats, malaise, cough and expectoration resulted in hospitalization in September 1956. Physical findings at this time were essentially normal. A chest roentgenogram revealed bilateral apical infiltrations and subsequent planigrams were interpreted as showing multiple cavities in both apices. Both histoplasmin and tuberculin (PPD .0001 mg.) skin tests were positive. Three sputa, three gastric washings

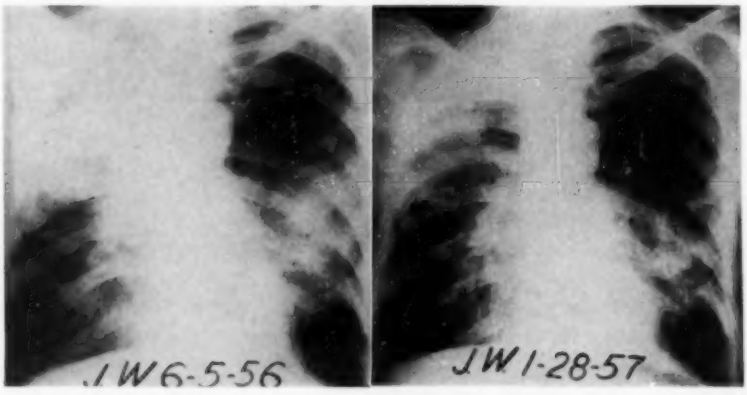

FIGURE 5A FIGURE 5B

Figure 5A (Case 18): Chronic progressive (cavitary) histoplasmosis with marked involvement of the right upper lobe. Prior to therapy.—*Figure 5B* (Case 18): Considerable clearing in both lungs, more marked on the right after oral amphotericin B supplemented with bi-weekly intravenous drug.

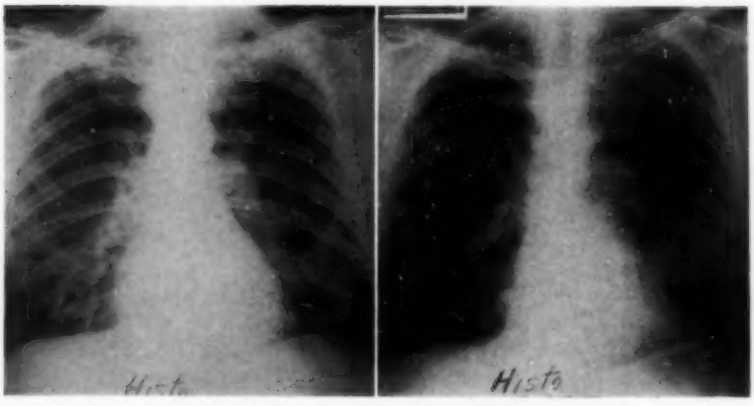

FIGURE 6A FIGURE 6B

Figure 6A (Case 15): Bilateral apical histoplasmosis with cavitation just prior to treatment.—*Figure 6B* (Case 15): Marked reduction in parenchymal disease after 3 months therapy with amphotericin B.

TABLE III
CHRONIC PROGRESSIVE PULMONARY HISTOPLAMOSIS
Summary of Clinical and Laboratory Data on Cases Treated with Amphotericin B

Case	Pre-Treatment: Clinical Condition	Pre-Treatment: X-Ray	Pre-Treatment: C. F. Titer	Pre-Treatment: Sputum Amount	Pre-Treatment: Sputum Culture	Regime: Route/Dose	Regime: No. Doses	Post-Treatment: Clinical Response	Post-Treatment: X-Ray Improvement	Post-Treatment: C.F. Titer	Post-Treatment: Sputum Amount	Post-Treatment: Sputum Culture	Comment
13. V. M. 42 W. M.	Fair	Far advanced Cavitation Bilaterally	1.32	30- 60 ml.	+	oral 4-6 gm. q.d.	330	Good	Slight to Moderate	1:16	5-10 ml.	0	Cavity (1.5 cm.) right sub apex disappeared. Cultures negative for 9 months
14. B. H. 64 W.M.	Poor	Far advanced Cavitation Bilaterally	1:256	30- 90 ml.	+	oral 4-8 gm. q.d. I.V. 100 mg. q.d.	240 9	Fair	Moderate Following I.V.	1:32	15-30 ml.	+	Improved remarkably, with I.V. drug —but received tetracycline at same time
15. M. K. 37 W. M.	Fair	Moderately Advanced Cavitation Bilaterally	1:8	50- 60 ml.	+	oral 4 gm. q.d. I.V. 50 mg. T.I.W.*	50 31	Good	Marked	1: 8	5-10 ml.	0	Febrile response following I.V. daily. Under therapy 4 months
16. C. J. 38 W. M.	Fair	Far advanced Cavitation Bilaterally	1:8	30- 60 ml.	+	oral 4 gm. q.d. I.V. 66 mg. T.I.W.	50 Good 31	Mod.	Moderate	0	3- 5 ml.	0	Under therapy 4 months 30 lb. weight gain
17. W. C. 35 W. M.	Fair	Moderately Advanced Non-cavity Apical disease	1:64	15- 20 ml.	+	oral 4-6 gm. q.d. I.V. 50 mg. T.I.W.	55 33	Good	Slight to Moderate	1:16	0	0	Improved on bed rest alone—further improvement following I.V. therapy —under therapy 4 months
18. J. W. 57 C. M.	Fair	Far advanced Cavitation Rt. upper lobe	1:32	90-100 ml.	+	oral 4 gm. q.d. I.V. 50 mg. B.I.W.**	84 48	Mod. Good	Moderate	1:16	30-40 ml.	0	Followed for 6 months since onset therapy

*T.I.W. = 3 times weekly. **B.I.W. = 2 times weekly.

and bilateral bronchial washings were negative on smear and culture for *M. tuberculosis*. Two sputa and the bronchial washings were cultured for fungi and all were positive for *H. capsulatum*.

After three months of bed rest and supportive therapy no significant change was noted and the patient was started on combined oral and intravenous amphotericin B as outlined in Table III. Under therapy he has shown a good clinical response with weight gain, disappearance of cough and marked reduction in sputum. Shortly after instituting therapy, *H. capsulatum* could no longer be isolated from the sputum despite repeated attempts. Figure 6 demonstrates the improvement on x-ray film after three months of amphotericin B.

3) *Severe Acute Pulmonary Histoplasmosis:* In light of the previously promising results a case with severe "epidemic" histoplasmosis was selected to observe the effect of the drug on the acute form of the disease. The prompt clinical response and fall in temperature and rapid clearing on x-ray film coincident with administration of the intravenous drug lead us to believe that they are causally related. It should be cautioned that the course is difficult to interpret since recovery is the rule in this form of histoplasmosis. On the basis of past experience it is our opinion that this illness was significantly shortened.

*Case 19:** This 49 year old white man was first seen on October 27, 1956, complaining of shaking chills and spiking temperatures to 104° F. (oral) of 12 hours duration. Persistence of these symptoms despite broad spectrum antibiotics led to his hospitalization two days later. A chest roentgenogram taken shortly after admission revealed a "diffuse" mottling throughout both lung fields (Figure 7A), whereas, a roentgenogram on admission was essentially negative. On the basis of clinical and epidemiological evidence a tentative diagnosis of acute "epidemic" histoplasmosis was made. *H. capsulatum* was subsequently isolated from gastric washings taken shortly after admission.

His course during the first six days of hospitalization was characterized by frequent shaking chills, drenching night sweats, fever to 104° F. and marked fatigue. On the fourth day moderate dyspnea was noted. By the seventh hospital day his general clinical condition had deteriorated and oral amphotericin B, 4 grams daily in divided doses, was given. After two days at this dosage level without demonstrable effect, the dosage was raised to 9.6 grams. Two days later the patient's condition appeared critical and intravenous therapy was instituted. Figure 8 presents his temperature curve demon-

*To be reported in detail by H. Rubin, P. H. Lehan, and M. L. Furcolow.

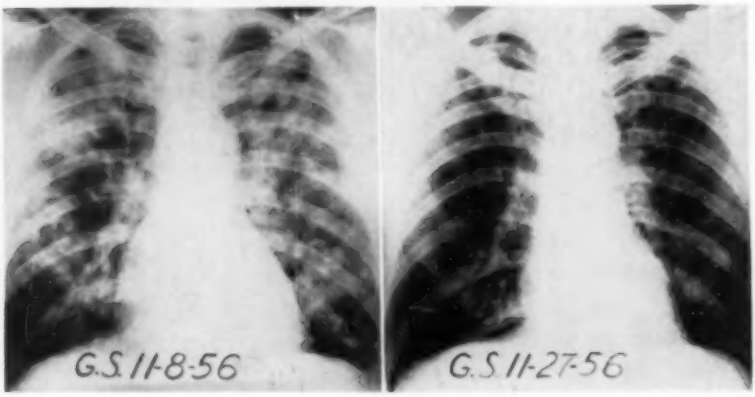

FIGURE 7A FIGURE 7B

Figure 7A (Case 19): Severe acute pulmonary histoplasmosis showing extensive disease as noted the day after therapy with intravenous amphotericin B was instituted.—*Figure 7B* (Case 19): Rapid resolution and clearing after 16 days therapy.

strating the rather dramatic drop in temperature coincident with the administration of the drug intravenously. After seven days it was decided to alter the therapeutic regime to every other day. It will be noted that with the temporary discontinuance of the drug there was a rise in temperature which again fell after therapy was reinstituted. His clinical response and clearing of pulmonary lesions paralleled his temperature curve (Figure 7B).

Dosage and Administration: The oral preparation used in these studies was administered as 200 mg. tablets of crystalline amphotericin B. Administration in dosages up to 8 grams daily presented no problem, however, poor absorption from the gastrointestinal tract makes this a questionable route of administration. Temporary improvement of several cases while under oral therapy indicate that this drug even in extremely low levels exerts some *in vivo* fungistatic effect.

Intravenous amphotericin B used in this series of cases was administered as a colloidal suspension (Estimated particle size 3 microns). The desired dose of amphotericin B was suspended in 5 per cent aqueous solution of dextrose in concentration of 1 mg. of drug per 5-10 cubic centimeters of water. Administration of the drug over a six hour period greatly reduced the incidence of side reactions. Studies by Louria et al.[25] indicate that amphotericin B serum levels of 0.7 to 1.5 mcg./ml. offered excellent protection and resulted in negative cultures of mice experimentally infected with H. capsulatum or C. neoformans. Using a modification of the bioassay technique described by Littman[27] comparable levels were obtained in humans receiving a dose equivalent to 1 mg./kg. body weight. Levels above 0.1 mcg./ml. were found to persist for approximately 18

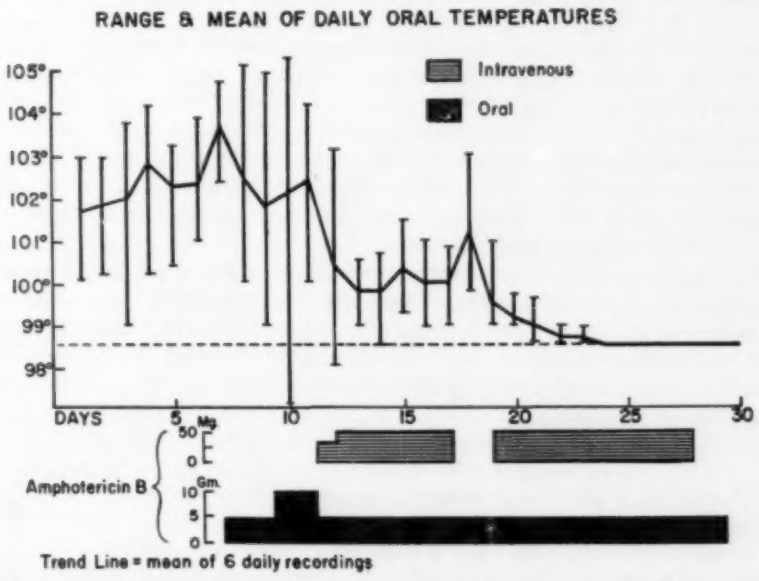

FIGURE 8 (Case 19): Depicts the temperature curve and response of severe acute pulmonary histoplasmosis to amphotericin B therapy. Note rapid fall in temperature curve following intravenous amphotericin B.

hours. One case receiving 1.7 mg./kg. maintained a serum level of 0.3 mcg./ml. for 30 hours after the drug was administered. From these data it is evident that a dose equivalent to at least 1 mg./kg. body weight is desirable. The persistence of the drug in the serum with higher doses indicates that such doses could be given every other day. Despite adequate amphotericin B serum levels, measurable spinal fluid levels (>.06 mcg./ml.) were not detected among the spinal fluids assayed.

Toxic Manifestations and Side Reactions: No evidence of either acute or chronic toxicity was noted in any of the patients receiving the oral form of amphotericin B. Several of these patients have received a total dose in excess of 1000 grams without ill effect. In several cases receiving intravenous therapy supplemented by oral drug, minor upper gastrointestinal symptoms and headache were noted.

The colloidal suspension of amphotericin B administered intravenously to the cases in this series resulted in several rather consistent undesirable side reactions. In almost every instance, shaking chills followed by a "spike" in temperature, during administration of the drug, was noted. It has been our experience that careful premedication with antihistaminics and antipyretics will reduce these to a minimum. Chemical phlebitis was troublesome but its incidence was not prohibitive if the drug was given slowly over a six hour period. In several instances the drug infiltrated into the surrounding subcutaneous tissues. Although this resulted in mild discomfort and redness at the site, no serious complication resulted.

Repeated hematopoetic, hepatic and renal function studies failed to show any evidence of toxicity. In only one (Case 4) was there evidence of possible toxic effect. In this case a transient rise in the blood urea nitrogen followed a dose of amphotericin B equivalent to approximately 1.4 mg./kg. This may have been related to persistent vomiting due to increased intra-cranial pressure and resultant dehydration. Following rehydration the blood urea nitrogen returned to normal. In this same patient the drug was discontinued earlier than planned because of the development of generalized pruritus.

Although only one of our cases showed a rise in the blood urea nitrogen, this rise has been noted by others using amphotericin B.[28] This finding was not accompanied by any other signs of renal toxicity and was only associated with higher doses of intravenous amphotericin B. Renal function, therefore, should be closely watched in those patients receiving doses above 1 mg./kg. of body weight.

Discussion

The present study conducted over the past several years was designed to "screen" promising antifungal agents. Both *in vitro* studies and clinical trials were employed to evaluate the therapeutic potentialities and toxicity of these agents. Clinical trials conducted on 38 patients with cryptococcal meningitis or progressive histoplasmosis with 2 hydroxystilbamidine, aminostilbamidine, MRD-112, mycostatin, and amebacide

have been disappointing. In only one patient was either clinical improvement or cultural conversion attained.

Among the patients treated with amphotericin B preliminary results were dramatic with both clinical improvement and cultural conversion. Poor absorption from the gastrointestinal tract make the present oral preparation of only questionable value. Studies are now under way to find some means of enhancing absorption from the gastrointestinal tract. The intravenous preparation is moderately well accepted by the patient in its present state and "adequate" blood levels are easily obtainable. The problems of short follow-up periods and spontaneous remissions even among those forms of mycotic infections generally considered fatal must be considered. This may well account for the response noted in any single case treated with amphotericin B. It is, however, unlikely that this can explain the consistently favorable response and conversion of cultures in all patients receiving significant amounts of intravenous drug. It is difficult to explain the dramatic response obtained in cryptococcal meningitis in light of our inability to demonstrate drug levels in the cerebro-spinal fluid. It may be only small amounts of drug are necessary and the bioassay technique employed does not detect such levels. *In vitro* studies and clinical trials now under way in patients with blastomycosis and coccidioidomycosis indicate that this agent may well be a "broad spectrum" antifungal antibiotic.

The moderate x-ray improvement noted among those with chronic progressive cavitary histoplasmosis is not surprising if one considers the underlying pathologic changes. The fact that marked reduction in sputum and cultural conversion was attained is considered to be a highly significant finding. Recently we have followed some 30 cases of chronic progressive pulmonary histoplasmosis with frequent cultures for varying periods up to two years. Of the 300 cultures performed, *H. capsulatum* was recovered in 75 per cent of the specimens.[29] It appears to us that the therapy of histoplasmosis with amphotericin B may well be in the same stage as that of tuberculosis in the early streptomycin era. Combined drug therapy may be the solution to the problem.[30] Although surgery has been of definite value in appropriate cases, fear of complications with an organism resistant to therapy has been a major deterrent to this approach. The availability of a specific therapeutic agent will undoubtedly make this approach more feasible.

SUMMARY

Experiences with the treatment of over 60 cases of deep mycotic infections with seven antifungal agents are reviewed. Favorable results in the treatment of cryptococcal meningitis and histoplasmosis with a new antibiotic, amphotericin B, are reported.

RESUMEN

Seis agentes antimicósicos prometedores *in vitro* se emplearon en ensayos clínicos en 60 enfermos con micosis profundas, progresivas para

valuar su eficacia terapéutica y la toxicidad. No se pudo demostrar efecto terapéutico sobre la histoplasmosis o sobre la criptococcosis en los ensayos empleando B dietiloaminoetil fencolato (MRD-112, Merrell), 2 hidroxi 4, 4: estilbenedicarboxamida (2-hidroxistilbamidina, Merrell), 2 amino 4, 4′ estilbenedicarboxamida (2-hidroxistilbamidina, Merrell), fenoxi etano dihidroclorhidrato (amebecida Lilly).

Se obtuvieron respuestas favorables en la blastomicosis generalizada usando 2 hidroxi 4, 4 estibenedicarboxamida.

Los resultados obtenidos preliminarmente con nuevo antibiótico, amfotericina B (Fungizona Squibb), en 19 casos de meningitis de criptococos y en histoplasmosis se relatan. Los enfermos tratados con anfotericina B demostraron mejoría clínica y radiológica. Los especímenes clínicos viraron a la negatividad después del tratamiento con amfotericina B. Este antibiótico demostró ser relativamente no tóxico y ofrece la primera esperanza de una terapéutica específica para estas afecciones micósicas.

RESUME

Six médications antimycosiques, efficaces *in vitro* furent essayées cliniquement chez 60 malades atteints d'infections mycosiques sévères progressives, pour évaluer leur effet thérapeutique et leur toxicité. On ne put mettre en évidence aucun effet thérapeutique sur l'histoplasmose ou la cryptococcose pendant ces essais, tant avec le B diethyl-aminoethyl fencolate (MRD.112, Merrell), le 2 hydroxy 4, 4′ stilbenedicarboxamide (2-hydroxystilbamidine, Merrell) le 2 amino 4, 4′ stilbenedicarboxamide (aminostilbamidine, Merrell) la "nystatine" (mycostatin, Squibb) qu'avec le 1, 2 bis para (n-hexyl methylaminomethyl) phenoxy ethane dihydrochloride (amebacide, Lilly). On obtint des réponses thérapeutiques favorables avec le 2 hydroxy 4, 4′ stilbenedicarboxamide.

Les auteurs rapportent les résultats préliminaires obtenus avec un nouvel antibiotique, l'amphotéricine B (fungizone, Squibb) dans 19 cas de méningite cryptococcique, et d'histoplasmose progressive. Les malades traités par l'amphotéricine B intraveineuse présentèrent une amélioration clinique et radiologique. Les produits provenant des malades devinrent négatifs après traitement par l'amphotéricine B. Cet antibiotique se montra relativement peu toxique, et offre le premier espoir d'un agent thérapeutique spécifique pour ces infections mycosiques.

ZUSAMMENFASSUNG

Es wurden 6 gegen Pilzerkrankungen gerichtete Stoffe, die in vitro eine Wirksamkeit versprachen zu klinischen Versuchsreihen benutzt, die an 60 Patienten mit fortschreitenden tiefen mykotischen Infektionen ausgeführt wurden, zur Auswertung von deren therapeutischem Effekt und Toxizität. Eine therapeutische Wirksamkeit konnte nicht beobachtet werden bei der Histoplasmose oder Kriptococcose bei den Versuchsreihen mit B diethylaminoethyl fencolat (MRD-112, Merrell) 2 hydroxy 4,4′ stilbenedicarboxamid (2-hydroxystilbamidin, Merrell), 2 amino 4,4′ stilbenedicarboxamid (aminostilbamidin, Merrell), nystatin (mycostatin, Squibb),

und 1,2 Bis para (n-hexyl methylaminomethyl) phenoxy ethane dihydrochlorid (amebacid, Lilly). Günstige therapeutische Reaktion bei generalisierter Blastomycose wurde bewirkt durch Verwendung von 2 hydroxy 4,4′ stilbenedicarboxamid.

Vorläufige Ergebisse wurden vorgelegt, die mit einem neuen Antibioticum, Amphotericin B (Fungicon, Squibb) an 19 Fällen mit Cripticoccen-Meningitis und progredienter Histoplasmose erzielt wurden. Mit Amphotericin B intravenös behandelte Patienten bewiesen klinische und röntgenologische Besserung. Klinische Untersuchungsproben wurden negativ nach Behandlung mit Amphoericin B. Dieses Antibioticum erwies sich als relativ nicht toxisch und bietet die erste Hoffnung auf eine spezifische therapeutische Substanz gegen diese Pilzinfektionen.

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A Disposable Unitized Plastic Sheet Oxygenator for Open Heart Surgery*

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Since 1955, more than 350 patients have undergone direct vision intracardiac surgery at the University of Minnesota Hospitals utilizing a pump oxygenator of the bubble type.[1, 2, 3]

Because of the simplicity, reasonable cost, and eminently satisfactory performance of this oxygenator, we have sought to adapt its principle features in an equally effective oxygenator which could be commercially manufactured in quantity. Attainment of this objective promises not only to facilitate the performance of open cardiac surgery in those centers where it is already in progress, but also to widen the applicability of the benefits of open cardiotomy in many other areas. Moreover, there are innumerable potential applications for a readily available pump oxygenator system in the treatment by partial cardiopulmonary bypass of medical emergencies coincident with a failing myocardium (coronary thrombosis) or reversible pulmonary disease (edema, infection) as well as for the resection of certain aneurysms and unusual tumors.

The Oxygenator

This unitized oxygenator is constructed of two sheets of polyvinyl plastic. The desired channels and chambers are delineated by a heat seal of the plastic material (Figure 1). It incorporates the same chambers as its three dimensional prototype. There is a vertical mixing tube, a siliconized debubbling chamber, and a series of three short inclined columns (settling chamber) for the final removal of any remaining free gas. This two dimensional modification of the helical settling chamber has proved completely dependable as a barrier to the downward progression of bubbles. The oxygenator is a self-contained unit with an oxygen disperser heat-sealed into the lower end of the mixing chamber, a saran filter fabricated into the exit of the settling chamber, and a thermostat pocket built into the arterial (settling) chamber to facilitate heat regulation. Two venous inflow tubes enter the lower mixing chamber. One tube is the main inlet to the oxygenator for venous blood from the cavae and the other tube permits the entrance of blood aspirated by the cardiotomy sucker into the mixing chamber. The arterial outflow tube returns the arterialized blood from the oxygenator to the patient.

The complete oxygenator is suspended from a dynometer spring scale,†

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†Chatillon Scale #806, John Chatillon & Son, Co., New York, N. Y.

making it readily possible to maintain the blood volume of the unit quite constant.

The heat source may be obtained either from a set of three heat lamps** (Figure 2) or a heating element contained in a reflecting pan.† Either is automatically controlled by a simple thermostat and relay switch‡ contained in the thermostat pocket (Figure 1). A thermometer may be inserted

**G. E. reflector infrared heat bulbs (clear glass), 250 watts each.
†Volco Heating Company, Minneapolis, Minnesota.
‡Travenol Division of Baxter Laboratories, Inc., Morton Grove, Illinois.

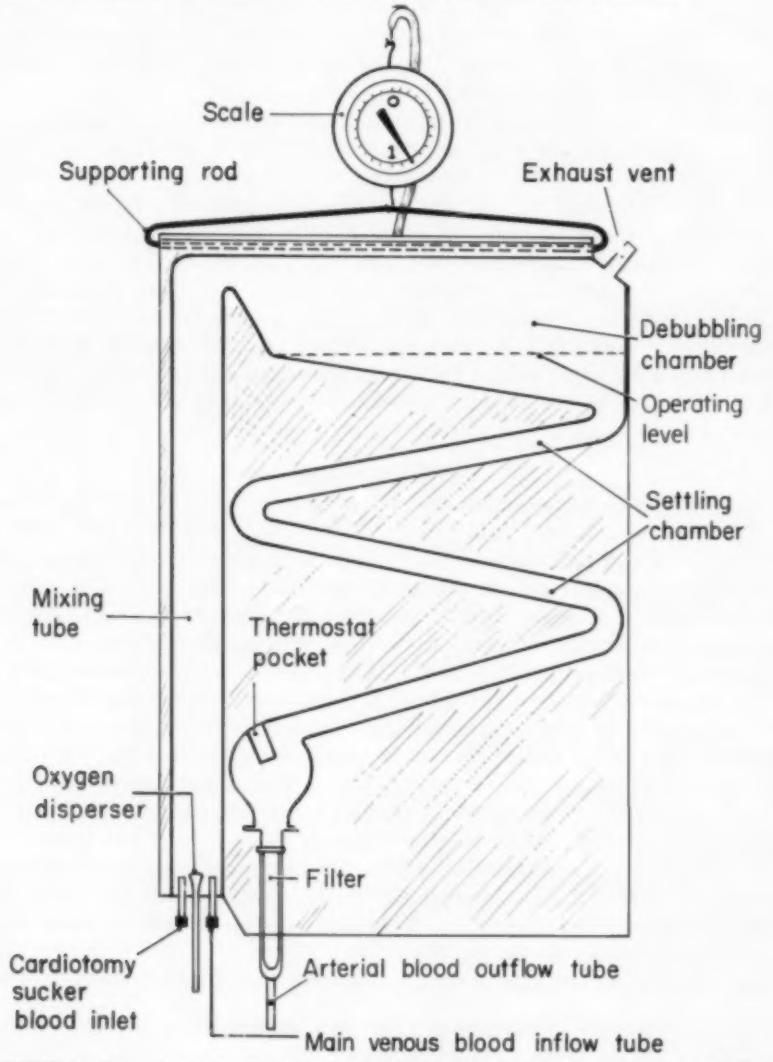

FIGURE 1: Diagrammatic illustration of the plastic sheet oxygenator suspended from the spring scale.

into this same pocket for manual regulation of the heat source. The oxygenator is commercially available,‡ and comes packaged as a ready to use sterile unit containing antifoam in the debubbling chamber.

The oxygenator described herein evolved through a continuing modification of several designs tested in more than 74 dogs.[4] It has been utilized in eleven clinical cases to date and the results of these perfusions are presented herein.

Methods

The clinical trials of this oxygenator have been in conjunction with the Sigmamotor pump§ (multiple cam activated metal fingers). The pump

‡Travenol Division of Baxter Laboratories, Inc., Morton Grove, Illinois.
§Sigmamotor, Inc., Middleport, New York.

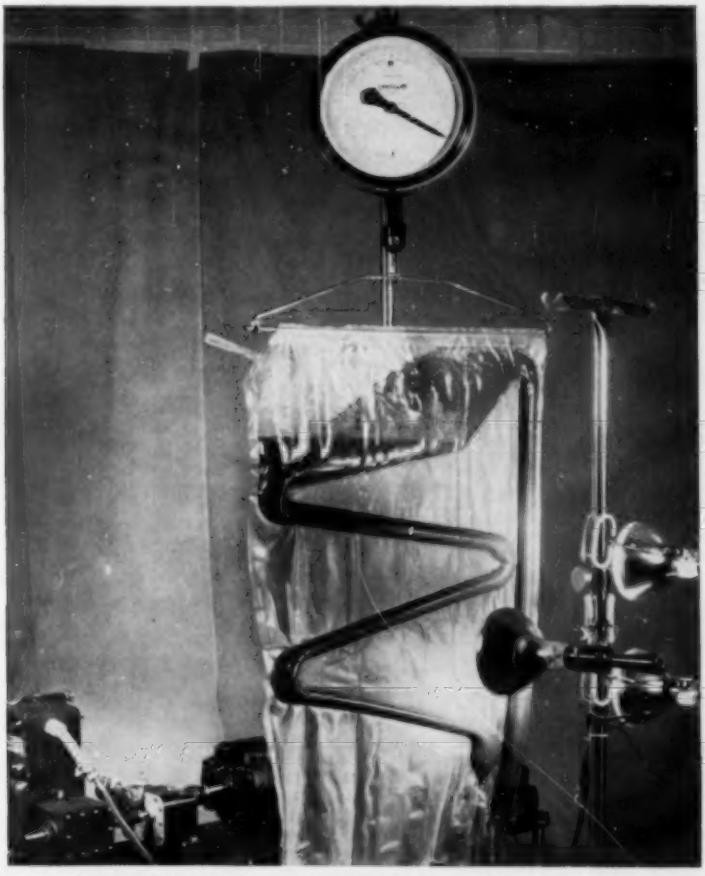

FIGURE 2: Photograph of the sheet oxygenator in combination with the Sigmamotor pump. Note: the suspending spring scale which allows instantaneous assessment of the blood volume. Heat loss is being controlled by the three heat lamps directed on the settling chamber. These lights are automatically turned on and off as necessary by the simple thermostatic relay switch inserted in the special pocket.

oxygenator connections¶ are diagrammed in Figure 3. This diagram also depicts the gravity venous drainage system and the cardiotomy blood return system. This cardiotomy return unit permits aspiration of the coronary sinus blood, returning it promptly to the oxygenator circuit. The collection of systemic venous blood by gravity drainage rather than pump suction offers several advantages.[5] It prevents a periodic rise in the venous pressure due to caval flutter (occasioned by the pliable caval walls being sucked against the venous catheters), and provides a more stable flow, minimizing the adjustments of the venous pump during the perfusion. If desired, the venous pump can be eliminated by dropping the oxygenator inlet to a level 10-12 inches below that of the right auricle. The arterial head of the pump is set to deliver 50-75 cc./kilogram/minute and may be increased during the perfusion if the monitoring electro-encephalogram

¶Stainless steel connectors specially designed to obviate blood trauma available from Phelan Mfg. Co., Minneapolis, Minnesota.

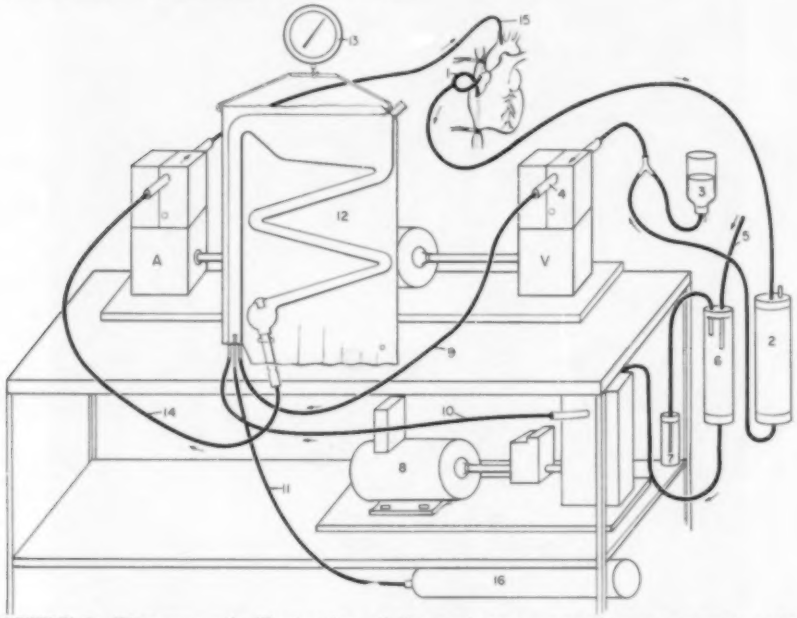

FIGURE 3: Diagrammatic illustration of the extracorporeal pump-oxygenator circuit. 1) Vena caval catheters,* 2) gravity venous drainage reservior,** 3) blood reservoir (standard blood bottles), 4) Latex hose, 5) tubing** from cardiotomy sucker, 6) cardiotomy sucker reservoir (disposable polyvinyl plastic**), 7) mercury suction trap to regulate pressure in cardiotomy sucker system, 8) cardiotomy sucker pump (Sigmamotor model T-65), 9) venous inflow tubing,** 10) cardiotomy sucker blood inflow tubing,** 11) gas line,** 12) plastic sheet oxygenator, 13) dynometer scale, 14) arterial outflow tubing,** 15) arterial cannula,* 16) tank containing 100% oxygen. All latex rubber and polyvinyl plastic tubing are sterilized by steam autoclaving and are discarded after each use as is the oxygenator unit. Only the stainless steel adaptors and connectors are cleaned and reused.

*Autoclavable plastic catheters designed and internally polished specifically for this use are obtained from C. R. Bard, Inc., Summit, New Jersey.
**Polyvinyl plastic, Mayon Co., Hopkins, Minnesota.

and systemic blood pressure (obtained through a polyethylene tube in the internal mammary artery) show any significant changes. This range of flows, which depends upon the patient's age and the type of cardiac lesion, permits adequate tissue oxygenation and also prevents any marked depletion of the bicarbonate level (alkaline reserve).[6, 7]

In eight clinical operations 100 per cent oxygen was used in the mixing tube of the oxygenator. A gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide was employed in the three cases. The mixture appears to maintain the pCO_2 at a more stable level than does the pure oxygen.

After suspending the oxygenator from the scale, the filter chamber should be filled with normal saline in a retrograde manner to eliminate air bubbles from this area, but the arterial pH was depressed. Thus, we currently favor the use of 100 per cent oxygen.

The oxygenator described herein is designed for flows to 1500 cc./minute and two pints of blood* are recommended for priming. After directing the heat lamps onto the oxygenator for two to three minutes the priming blood is introduced into the oxygenator through the mixing tube. This blood flows down the settling chamber and mixes with the few cubic centimeters of saline remaining in the filter chamber. The priming blood should be at or slightly warmer than body temperature for if the blood is substantially colder, the plasma may take up dissolved oxygen which can be released as gaseous emboli upon being warmed within the patient's body. It is emphasized that this precaution applies to oxygenators of all types and designs and constitutes the important reason for not allowing the blood temperature in the oxygenator to drop below the patient's temperature during perfusion.

After giving the patient 1½ mg./kilogram of heparin** the great vessels are cannulated and the connections to the pump oxygenator are made (Figure 3). Henceforth until perfusion has ceased and the protamine is given all blood transfused into the patient or into the extracorporeal circuit is heparinized. Before and after this interval the standard citrated bank blood is used for whatever replacement may be necessary.

As the perfusion starts venous blood enters the mixing chamber and the gas flow is adjusted so that a gentle uninterrupted column of bubbles rises in the mixing tube. Usually a gas flow of 2.5 to 5 liters/minute is sufficient but this consideration is dependent upon the blood flow rate. The presence of a churning motion or of clear areas in the mixing tube indicates that the oxygenating gas is entering too slowly or too fast, respectively, for that particular blood flow rate. The blood level in the oxygenator unit is maintained such that the lower ⅓ of the debubbling chamber remains filled with blood (Figure 1).

On completion of the perfusion, protamine sulfate is given to the patient in a dosage of twice the amount of heparin given. We have not found the performance of heparin-protamine titrations to be necessary.

*This blood is drawn into siliconized bottles (600 cc.'s) with 20 mg. heparin contained in 30 cc. of saline as the anticoagulant. These bottles are commercially available from Travenol Division of Baxter Laboratories, Inc., Morton Grove, Illinois.

**Patients weighing more than 35 kilograms should receive 2 to 2.5 mg. heparin/kilogram of body weight.

Results

The observations recorded in these first eleven patients having open cardiotomy utilizing this oxygenator are presented as follows.

Biochemical Observations During Perfusions

Five arterial blood samples have uniformly been drawn during these operations as indicated in Table I.

Sample 2 (Table I) was drawn about three minutes after perfusion began. This allowed time for entrance of the patient's blood into the oxygenator. The average time for sample 3, drawn after repair of the defect, was 20½ minutes and the average time for sample 4, drawn from the oxygenator on completion of the perfusion, was 27 minutes 20 seconds.

1. *Acid Base Changes*

The pH values of the arterial blood samples have been averaged for the eleven patients and are listed in Table I. The range of variation is indicated in the parentheses. Prior to the bypass the pH was usually elevated and as the perfusion proceeded it dropped gradually, attaining a near normal value at the conclusion of the bypass. A more precise measurement of the acid-base alteration, however, was the plasma bicarbonate level (alkaline reserve). The patient's average pre-perfusion level of bicarbonate was 19.10 mM/Liter. The bicarbonate level was 15.79 mM/liter (mean) in sample 2 drawn from the arterial limb of the pump three minutes after starting the perfusion. This drop in bicarbonate represents the mixing of the patient's blood with the slightly acidotic priming blood in the oxygenator. The bicarbonate level dropped an additional 3.74 mM/Liter (mean) during the remainder of the perfusion. These values are considered to be very reasonable considering the length of the bypass and the fact that no alkali was administered to these patients to restore the bicarbonate content of the blood. Part of this fall in plasma bicarbonate can be attributed

TABLE I
AVERAGE PERFUSION VALUES FOR PATIENTS USING THE POLYVINYL SHEET OXYGENATOR.

Sample Number		Average Time After Starting Bypass	Arterial pH	Arterial Plasma Bicarbonate at pH 7.4 (mM/L)	Venous Lactic Acid (mg. Per Cent)	Arterial Oxygen Saturation Per Cent	Plasma Hb (mg. Per Cent)
1	15 minute Pre-perfusion		7.50 (7.40-7.54)	19.10 (13.74-23.75)			
2	Perfusion started	3′	7.45 (7.28-7.58)	15.79 (10.28-18.73)	37.9 (31.5-50.5)		
3	Defect corrected	20′ 30″	7.41 (7.18-7.52)	13.50 (11.64-14.99)		96 (94-100)	
4	Perfusion concluded	27′ 20″	7.37 (7.15-7.50)	12.05 (8.28-13.81)	45.8 (33.0-61.4)	98 (94-100)	50 (28-79.6)
5	15 minute Post-perfusion		7.40 (7.32-7.48)	12.15 (9.96-14.30)			

to a rise in fixed acids as evidenced by the slight rise in the venous blood lactic acid level during the perfusion (Table I).

2. *Oxygenation of Venous Blood*

Satisfactory oxygenation of the venous blood was achieved. The oxygen saturation reached 96 per cent at the time the defect was closed and was measured at 98 per cent upon terminatioin of the bypass. This efficiency of gas exchange is a fundamental characteristic of bubble diffusion oxygenators.

3. *Hemolysis*

The average of the plasma hemoglobin values drawn at the end of the bypass in these eleven patients was 50 mg. per cent. From previous studies we know that some if not most of this low level of hemolysis can be attributed to the cardiotomy sucker unit rather than to the pump oxygenator. Usually 15 mm. of Hg. suction is applied to the cardiotomy reservoir, however when the intracardiac return is excessive it may be necessary to increase this amount of suction and the resulting hemolysis is usually correspondingly higher.

Operative Results

The performance of this sheet oxygenator was very satisfactory in all 11 perfusions. All patients were responsive and alert post-perfusion. Neither immediate nor remote neurologic sequelae were detected in any of the 11 patients. There were nine patients with isolated ventricular septal defects undergoing closure and two patients with pulmonary stenosis and other defects as indicated in Table II. Of the nine patients with ventricular septal defects, six are living and well (Table II).

Of the three patients not surviving, one child (J. M.) sustained a complete heart block during the closure of a ventricular septal defect. Two hours post-operatively while receiving Isuprel* treatment[8] she came out of block and developed sinus tachycardia with a rate of 240-260 beats/minute. Because the blood pressure was adversely affected by this severe tachycardia, digitoxin was administered despite the risk of precipitating a recurrence of the heart block. The rate dropped to 140 beats/minute and the blood pressure returned to normal levels, however she died of cardiac arrest eight hours post-operatively. Autopsy revealed complete closure of the ventricular septal defect and no other anatomic abnormality. Death was due to the sudden recurrence of complete heart block. Since the introduction of the myocardial electrode together with the artificial pacemaker for treatment of this complication, we have managed 18 patients with complete atrioventricular dissociation with only one death.[9]

Two other infants (T. S. and M. D.) each 12 months of age had severe pulmonary hypertension accompanying their ventricular septal defects. Both had uneventful operative procedures. Post-operatively they both had progressively increasing respiratory distress with death ensuing 18 and 24 hours after surgery respectively. In each of these infants, autopsy confirmed the complete and correct closure of the septal defects. In both

*Isopropyl levo arterenol, Winthrop Laboratories, New York, New York.

TABLE II

RESULTS FOR FIRST 11 PATIENTS HAVING DIRECT VISION INTRACARDIAC SURGERY UTILIZING PLASTIC SHEET OXYGENATOR

Patient Age, Weight	Defect	Pressures		Duration of Perfusion	Perfusion Rate cc./min.	Operative Procedure	Results
		Pul. Art.	Sys. Art.				
W. S. 2 yr. 9.8 Kg.	7 mm. IVSD	42/13	110/70	26′ 37″	600	Heart arrested with K citrate and polyvinyl sponge* sutured into defect for closure	Living and well
T. S. 1 yr. 6.4 Kg.	25 mm. IVSD	110/ 0 Rt. V.	115/60	30′ 48″	400	Polyvinyl sponge sutured into defect for closure	Awake and alert P.O. Resp. distress progressing until death 18 hrs. later. Severe pul. arteriolar intimal proliferation at autospy
D. P. 14 mo. 7.2 Kg.	5 mm. IVSD	48/20	110/70	17′ 17″	470	Polyvinyl sponge sutured into defect for closure	Living and well
M. B. 1 yr. 8.0 Kg.	Pul. st. & 12 mm. IVSD	20/10	90/56	15′ 25″	500	Stenotic pulmonary valve repaired through pul. arteriotomy exploratory rt. ventriculotomy	Awake and alert P.O. Died suddenly 8 hrs. P.O.12 mm. IVSD at autopsy visible only from left side of septum
S. T. 3 yr. 11.2 Kg.	30 mm. IVSD	60/30	120/70	35′	600	Heart arrested with K citrate & polyvinyl sponge sutured into defect for closure	Living and well
J. M. 7 yr. 15.9 Kg.	35 mm. IVSD	63/18	120/70	41′ 3″	850	Heart arrested with K citrate and polyvinyl sponge sutured into defect for closure	Patient sustained complete A-V block at surgery. Died 8 hrs. P.O.
M. D. 1 yr. 6.1 Kg.	12 mm. IVSD	62/16	70/40 (desat.)	31′ 8″	360	Polyvinyl sponge sutured into defect for closure	Awake and alert P.O. Severe resp. distress progressing until death 24 hrs. P.O. Severe pul. art. intimal proliferation at autopsy
J. M. 1 yr. 8.2 Kg.	5 mm. IVSD	36/10	104/70	22′ 5″	500	Polyvinyl sponge sutured into defect for closure	Living and well
C. B. 4 yr. 16.6 Kg.	15 mm. IVSD	42/19	95/75	24′ 31″	750	Heart arrested with K citrate and polyvinyl sponge sutured into defect for closure	Living and well
R. B. 9 yr. 20.2 Kg.	15 mm. IVSD	78/37	95/70	38′ 33″	900	Heart arrested with K citrate and polyvinyl sponge sutured into defect for closure	Living and well
P. T. 4 yr. 14.4 Kg.	Pul. st. & I.A.S.D. (secundum)		110/70	17′ 6″	650	Stenotic pulmonary valve repaired via pulmonary artery. Atrial septal defect closed with interrupted sutures by atriotomy	Living and well

*Ivalon, Clay Adams, Inc., New York, New York.

patients microscopic study of the lungs disclosed advanced intimal proliferation of the pulmonary arterioles. Death of these infants was due to circulatory failure resulting from the high resistance in the pulmonary circuit. We have previously emphasized the factors responsible for an increased operative risk for infants requiring open heart surgery at an early age.[10]

The two other patients operated upon had pulmonary stenosis associated with an atrial septal defect in one instance (P. T.) and a ventricular septal defect in the other (M. B.). The former survived and the latter did not. This last patient (M. B.) was particularly instructive. She had a preoperative diagnosis of isolated valvular pulmonary stenosis. The preoperative studies had included both cardiac catheterization and angiocardiography. At surgery, this defect was present and was repaired under direct vision through a pulmonary arteriotomy. However, the surgeon suspected the possibility of additional defects in this infant because the clinical disability had been much more severe than one could have expected from the degree of valvular pulmonic stenosis found. Therefore, a short ventriculotomy incision was made to allow direct vision inspection of the ventricular septum and insertion of a finger through the tricuspid valve to palpate the atrial septum. No defects were detected by these maneuvers. The patient died suddenly eight hours after surgery. Post-mortem examination demonstrated a sizeable ventricular septal defect in this infant (12 mm. in diameter), visible only from the left side of the septum, for it was obscured completely by hypertrophied trabeculations of the right ventricle. (The pathologist also missed detecting this defect until later when the left ventricle was opened.) Since this chastening lesson, these concealed ventricular septal defects have been correctly diagnosed by injecting through a needle, Evans blue dye (T-1824) into the left ventricle (and momentarily compressing the aorta between the fingers) after performing the right ventriculotomy. If there is a ventricular septal defect obscured by hypertrophied trabeculations or located in an unusual site, the dye will make the defect apparent.

Discussion

The oxygenator described in this report appears to be equally as effective as its three dimensional prototype. Values for oxygenation, acid-base shift and hemolysis are comparable to those measured during 250 clinical perfusions with the previously described bubble oxygenator.[6, 7]

The technique of suspending the oxygenator from a spring scale provides an accurate and practical method for maintaining a constant blood volume in the patient. It is important to note that in perfusions carried out in seriously ill infants weighing a few kilograms, there is at best a narrow margin between success and failure, and an imbalance of as little as several ounces of blood in either direction may be crucial in determining success or failure.

The oxygenator described herein effectively accommodates flows up to 1500 cc./minute. At the present time we are completing the experimental evaluation of a larger model of the same design which is capable of han-

dling effectively blood flows up to four liters/minute. There have been no obstacles encountered in the experimental perfusions evaluating this larger unit.

CONCLUSIONS

1. A unitized, disposable, inexpensive bubble diffusion oxygenator constructed of two sheets of polyvinyl plastic has been used successfully in 11 clinical cases.

2. This oxygenator is commercially available as a sterile packaged unit ready to hang up, prime, and use.

3. Seven of 11 patients had intracardiac defects completely corrected and are living and well at this time. The remaining four patients (three were seriously ill infants) succumbed from complications including pulmonary hypertension and complete atrio-ventricular heart block. In none of these four patients did it appear that the performance of the pump or oxygenator could be incriminated in the unsuccessful outcome.

4. Biochemical perfusion data on these 11 patients compares favorably with determinations made on 250 patients perfused with the three dimensional prototype of this unit.

RESUMEN

1. En once casos clínicos se ha usado satisfactoriamente un oxigenador construido con dos hojas de polivinil. Es unificado, puede descartarse una vez usado, no es costoso y funciona por difusión de burbujas.

2. Este oxigenador se puede obtener comercialmente para usarseen un paquete esterilizado, para colgarse, prepararse y ponerse a funcionar.

3. De once enfermos con defectos intracardiacos siete se corrigieron completamente, están vivos y bien al presente. Los cuatro restantes (tres niños gravemente enfermos) sucumbieron debido acomplicaciones incluyendo hipertensión pulmonar y bloqueo cardiaco completo, atrioventricular.

En ninguno de estos cuatro enfermos pareció que el trabajo del oxigenador o de la bomba pudiese ser causante del mal resultado.

4. Los datos bioquímicos de la perfusión de estos once enfermos se comparan favorablemente con las determinaciones hechas en 250 enfermos perfundidos con el aparato prototipo, tridimensional de esta unidad.

RESUME

1. Un oxygénateur à barboteur, bon marché, maniable, composé de deux feuilles de polyvinyle, a été utilisé avec succès dans onze cas cliniques.

2. Cet oxygénateur est présenté dans le commerce en paquet stérile, prêt à l'emploi.

3. Sept des onze malades avaient des malformations intracardiaques complètement corrigées, et sont maintenant en vie et en bonne santé. Les quatre autres malades (dont trois étaient des bébés gravement atteints) succombèrent de complications comprenant l'hypertension pulmonaire et un syndrome d'Adam-Stokes atrio-ventriculaire. Chez aucun de ces quatre malades, il n'apparait que l'on puisse mettre en cause le functionnement de la pompe ou de l'oxygénateur dans l'issue fatale.

4. Les données biochimiques de la perfusion chez ces onze malades peuvent être comparées favorablement à celles qui ont été dèterminées chez

250 malades, qui reçurent des perfusions avec le prototype à trois dimensions de ce service.

ZUSAMMENFASSUNG

1. Es wurde ein vereinheitlichtes leicht verfügbares, wohlfeiles Sauerstoffgerät mit Sprudel-Diffusion hergestellt aus 2 Plastikscheiben und Polyvinyl, und in 11 klinisch behandelten Fällen erfolgreich eingesetzt.

2. Dieser Oxygenator ist im Handel erhältlich in vollständig steriler Verpackung, fertig zur Befestigung, Aufladung und Benutzung.

3. Bei 7 von 11 Kranken wurden intracardiale Fehler in vollem Umfange korrigiert und alle sind am Leben und fühlen sich bis jetzt wohl. Die restliche 4 Kranken, von denen 3 schwer kranke Kinder waren, erlagen Komplikationen einschliesslich pulmonalem Hochdruck und komplettem atrioventriculärem Herzblock. Bei keinem dieser 4 Patienten hatte es den Anschein, als ob die Tätigkeit der Pumpe oder des Sauerstoffgerätes als Ursache für die erfolglosen Verläufe angeschuldigt werden könnte.

4. Biochemische Durchströmungswerte von diesen 11 Patienten stimmen gut mit bei 250 Patienten gefundenen Werten überein, bei denen die Sauerstoffversorgung mit dem dreidimensionalen Typ dieses Gerätes vergenommen worden war.

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Prolonged Blood Levels with Sustained Action PAS*

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It is recognized that para-aminosalicylic acid is a drug of major importance in the treatment of tuberculosis. PAS is an effective bacteriostatic agent per se,[1-5] and when administered in proper dosage delays the emergence of streptomycin or isoniazid resistant strains of tubercle bacilli.[6-8] These actions of PAS serve as a basis for the combined and prolonged chemotherapy of tuberculosis.[9-12]

However, patient intolerance to standard preparations of PAS frequently limits its use in a significant number of cases, necessitating drug discontinuance or decrease in dosage. The intolerance is manifested by gastrointestinal irritation, including abdominal distress, nausea, vomiting, abdominal pain, diarrhea, or any combination of these symptoms. Several reports[13-14] indicate that approximately 25 per cent of patients are unable to tolerate full doses of PAS primarily because of these adverse gastrointestinal symptoms. Various PAS preparations have been tried in order to overcome these disturbing side effects. It has been demonstrated that the administration of buffered PAS,[15] potassium or calcium salts of PAS,[16-18] as well as resin PAS,[19] tend to reduce the gastrointestinal side-reactions encountered during therapy with para-aminosalicylic acid or sodium PAS solution and tablets.

Morse et al,[20] Mandel et al,[21] have recently demonstrated that the concomitant administration of PAS with isoniazid results in increased biologically active isoniazid blood levels. Thus, high and sustained PAS blood levels tend to potentiate the antituberculous activity of serum isoniazid. In view of these observations, it is apparent that an essential prerequisite of the ideal PAS preparation, in addition to its maximum toleration, is its ability to maintain optimum therapeutic blood level concentrations throughout the entire 24 hour period of treatment.

In a previous report,[22] we have indicated that sustained action PAS tablets (Parasal—S.A. 1.0 Gm., Sodium free) are well tolerated by patients unable to take other PAS preparations. The sustained action tablets produced less frequent and milder gastrointestinal disturbance, if any, than other preparations in current use, i.e., sodium and potassium salts, buffered or granular forms of PAS.

The sustained action tablet consists of two layers containing a total of 1.0 Gm. of PAS, sodium free. The sugar coated outer layer contains 0.5 Gm. of buffered PAS† which readily disintegrates within the stomach and

*The sustained action PAS tablets used in this investigation were generously supplied as Parasal—S. A. Tablet 1.0 Gm., by The Panray Corporation, New York, New York.

**From the Chest Section, Medical Service, Veterans Administration Hospital.

†The buffer consists of dihydroxy aluminum acino-acetate and calcium carbonate.

is rapidly absorbed. The inner core, covered by a delayed action coating, contains 0.5 Gm. of pure PAS for intestinal absorption. It is postulated that the differential absorption of PAS between the stomach and the intestinal tract provides sustained PAS blood levels, and prevents irritating high local PAS concentrations within the gastrointestinal tract. These factors, in addition to the buffer in the outer layer, may account for the improved tolerance.

Method of Study

The subjects selected for this study were all men with pulmonary tuberculosis, ranging in age from 20 to 50 years. They were in good physical condition and presented no evidence of impaired renal function or other associated diseases. All medications were discontinued for at least three days prior to the testing period.

In order to determine the effect of dosage and of the interval of administration of the sustained action tablets on the PAS blood concentration, 38 patients were divided into four groups as follows:

A) Ten received a single dose of four grams (4 tablets) at 8:00 A.M. The blood specimens were taken at 1-2-3-4-6, and 8 hours after administration of this single dose.

B) Nine whose dosage was four grams three times daily at six hour intervals (7:00 A.M., 1:00 P.M., and 7:00 P.M.).

C) Nine were given three grams (3 tablets) t.i.d. at six hour intervals (7:00 A.M., 1:00 P.M., and 7:00 P.M.).

D) Ten received four grams t.i.d. every eight hours (8:00 A.M., 4:00 P.M., and 12:00 P.M.).

To stabilize the blood levels, the patients in groups B, C, and D received the sustained action PAS tablets for at least three days prior to determination of the blood concentrations. In each case, blood specimens were taken at 1-2-3-4-6, and 8 hours after administration of the second dose of the day. In addition, blood specimens were obtained at 7:00 A.M. the following day prior to the administration of the initial morning dose.

The serum PAS concentration was determined by the method of Deeb and Vitagliano.[15] All determinations were performed on freshly prepared serum and duplicate analyses were made on all specimens. In each instance, the PAS serum concentration represents the average of these duplicate findings. A total of 520 determinations were made in this group of 38 patients.

In addition, each case was carefully observed for toleration of the drug and its acceptance. All signs and symptoms of gastrointestinal irritation incident to this drug were particularly noted.

Results

The serum levels of PAS following administration of a single four gram dose of sustained action PAS tablets are shown in Table I. After the first hour the serum PAS concentration averaged 5.1 mg. per cent with progressive decline in levels during the subsequent hours. It is noted that a therapeutic concentration of PAS is present for only two to three hours

TABLE I
PAS BLOOD SERUM CONCENTRATIONS (MGM. PER CENT) FOLLOWING A SINGLE 4 GM. DOSE OF SUSTAINED ACTION PAS TABLETS

	Hours After Drug Administration					
Case	1	2	3	4	6	8
1	4.3	2.8	1.5	0.9	1.0	0.5
2	3.1	1.9	1.2	1.1	0.8	0.4
3	9.3	....	2.8	....	0.9	....
4	4.8	2.0	1.0	0.7	0.5	0.5
5	6.2	2.6	1.1	0.4	0.4	0.4
6	....	2.6	1.5	0.8	1.1	0.6
7	5.3	2.0	0.9	0.4	0.4	0.4
8	5.5	2.3	1.0	0.4	0.9	0.8
9	3.8	1.2	0.8	0.5	0.3	0.4
10	3.3	1.2	0.6	0.4	0.4	0.4
Average	5.1	2.1	1.2	0.6	0.7	.50

Table II demonstrates that multiple dosage of sustained action PAS tablets, four grams t.i.d. at six hour intervals, generally provided sustained therapeutic PAS serum levels for the entire 24 hours. Of significance, is the finding that the PAS serum concentration averaged 3.0 mg. per cent 12 hours after the evening dose, just prior to the initial morning dose. Early morning PAS blood levels, ranging from 7.0 to 2.2 mg. per cent, were present in seven of the nine cases. The accumulative effect of the multiple doses in this regimen apparently provided, in most instances, sustained and effective serum levels for the entire 24 hour period.

A decrease in dosage to three grams t.i.d. at six hour intervals (Table III) resulted in lower average PAS serum levels. However, these levels remained within the therapeutic range for approximately four to five hours. The early morning PAS serum level, prior to the initial daily dose, averaged only 1.0 mg. per cent. It appears, therefore, that this regimen of reduced dosage is not adequate for the maintenance of a 24 hour effective PAS level.

TABLE II
PAS BLOOD SERUM CONCENTRATIONS (MGM. PER CENT) FOLLOWING MULTIPLE DOSAGE WITH SUSTAINED ACTION PAS TABLETS. 4 GM. T. I. D. Q. 6 HOURS (7 A.M. - 1 P.M. - 7 P.M.)

	Hours After the Second Dose						
Case	1 (2 P.M.)	2	3	4	6 (7 P.M.)	9 P.M.	7 A.M.
11	6.3	4.7	3.5	3.3	2.3	5.3	2.2
12	3.3	4.7	5.2	4.5	2.7	6.0	3.4
13	5.3	4.3	5.9	5.6	3.1	6.2	2.5
14	4.3	5.3	3.4	2.4	1.6	4.4	2.3
15	17.1	16.4	16.0	12.9	10.9	13.8	7.0
16	10.1	10.9	9.8	8.8	6.0	9.3	3.9
17	10.0	11.9	11.5	10.2	9.2	15.1	3.7
18	8.0	8.4	5.9	4.3	2.6	7.6	0.7
19	5.9	6.5	5.8	5.3	3.3	10.4	0.9
Average	7.8	8.1	7.4	6.4	4.6	8.7	3.0
					Before 3rd Dose	2 Hrs. After 3rd Dose	12 Hrs. After 3rd Dose

TABLE III
PAS BLOOD SERUM CONCENTRATIONS (MGM. PER CENT) FOLLOWING MULTIPLE DOSAGE WITH SUSTAINED ACTION PAS TABLETS 3 GM. T. I. D. Q. 6 HOURS (7 A.M. - 1 P.M. - 7 P.M.)

Case	Hours After the Second Dose						
	1 (2 P.M.)	2	3	4	6 (7 P.M.)	9 P.M.	7 A.M.
20	4.2	3.0	2.2	1.7	1.0	2.9	1.5
21	3.9	3.0	1.5	1.1	0.5	2.5	0.4
22	2.3	3.0	2.4	2.9	2.3	3.3	0.5
23	1.1	2.0	1.6	1.9	0.8	2.1	1.2
24	5.3	3.6	1.8	1.2	0.6	3.1	1.2
25	4.2	4.7	4.3	2.6	0.9	4.1	0.8
26	4.3	2.9	1.4	0.9	2.7	5.1	....
27	4.3	4.5	3.7	3.7	1.9	3.4	1.4
28	5.5	5.3	4.1	2.8	1.6	6.5	1.0
Average	3.9	3.6	2.6	2.1	1.4	3.7	1.0
					Before 3rd Dose	2 Hrs. After 3rd Dose	12 Hrs. After 3rd Dose

The PAS serum concentrations following the administration of sustained action PAS tablets in dosage of four grams t.i.d. every eight hours are shown in Table IV. The average serum levels were generally within the therapeutic range. The PAS concentration at the end of eight hours after the second dose averaged 1.9 mg. per cent. Although sustained 24 hour PAS levels were obtained in most instances, this regimen necessitated the administration of the drug at late evening hours, rendering it inconvenient and impractical.

Figure 1 represents graphically the average PAS blood levels obtained with sustained action PAS tablets, four grams t.i.d. every eight hours, as compared to equivalent doses of sodium PAS solution given every four hours. For comparative purposes, the PAS blood levels for sodium PAS solution were selected from the results reported by Deeb and Vitagliano.[15] In this study the PAS blood levels were determined similarly after the second dose of the day. It is noted that the blood levels during the first

TABLE IV
PAS BLOOD SERUM CONCENTRATIONS (MGM. PER CENT) FOLLOWING MULTIPLE DOSAGE WITH SUSTAINED ACTION PAS TABLETS. 4 GM. T. I. D. Q. 8 HOURS (8 A.M. - 4 P.M. - 12 P.M.)

Case	Hours After the Second Dose					
	1	2	3	4	6	8
29	8.4	5.8	4.1	3.5	3.4	2.6
30	8.9	8.1	6.9	5.5	3.2	2.4
31	7.7	5.4	3.2	2.0	2.2	2.1
32	9.2	9.1	7.4	6.3	3.9	2.5
33	8.6	7.3	4.8	3.8	2.7	2.0
34	7.9	4.7	2.9	2.1	1.6	1.5
35	8.2	6.6	4.7	3.6	2.4	1.4
36	7.6	4.9	3.0	2.1	1.9	0.5
37	9.1	6.7	4.6	3.7	2.1	1.6
38	8.2	6.7	4.9	3.9	3.3	1.9
Average	8.4	6.5	4.7	3.7	2.7	1.9

hour after the administration of sodium PAS exceeded those obtained with sustained action tablets. Thereafter, the blood levels obtained with sustained action PAS tablets consistently exceeded those of sodium PAS solution. After the fourth hour, the blood levels resulting from sustained action tablets averaged approximately two to three times the values obtained with sodium PAS solution. Therapeutic blood levels were maintained with the sustained action tablets for approximately eight hours as compared with sodium PAS which provided an effective level for only a maximum of five hours.

Figure 2 graphically indicates the comparative average PAS blood levels obtained with multiple doses of the following: (a) sustained action PAS tablets—three grams t.i.d. at six hour intervals; (b) sustained action PAS tablets—four grams t.i.d. every six hours, and (c) sodium PAS solution—5.5 grams (4 grams free PAS) t.i.d. every four hours.[15] The blood levels were determined after the second and third doses of the day as indicated.

Figure 2 illustrates that sustained action PAS tablets in reduced dosage of three grams t.i.d. at six hour intervals maintained an effective blood level for about four to five hours, being equivalent to 5.5 grams of sodium PAS given t.i.d. every four hours.

Although, during the first hour sodium PAS solution produced an initially higher blood level, much higher concentrations were maintained subsequently with the four gram dose of sustained action tablets. The

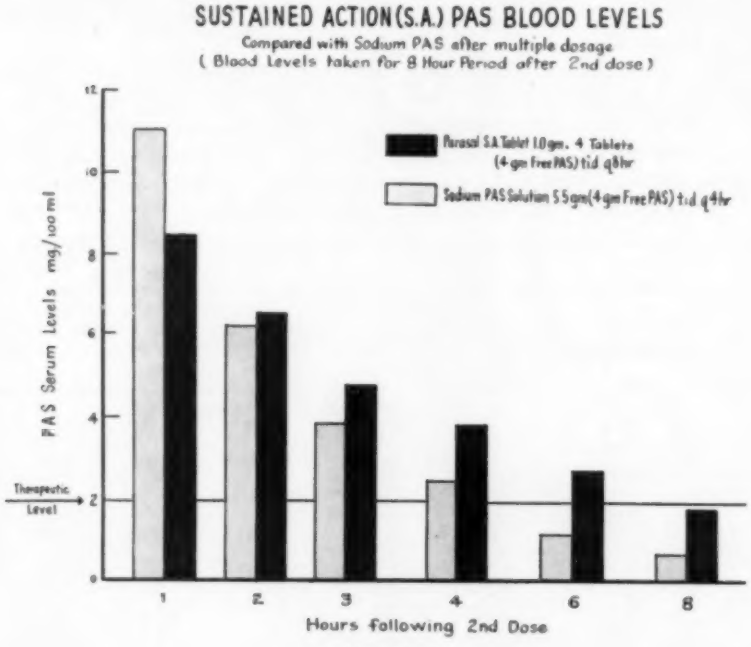

FIGURE 1

PAS levels after the fourth hour were approximately three times greater than those obtained with sodium PAS solution. Six hours following the administration of sodium PAS, the blood concentration was below the therapeutic level as contrasted with the effective level of 4.6 mg. per cent obtained with sustained action tablets. In addition, the 12 hour PAS level, prior to the initial morning dose averaged 3.0 mg. per cent with sustained action PAS. Thus, this PAS preparation, in dosage of four grams t.i.d. every six hours, maintained uninterrupted therapeutic blood concentrations for the entire 24 hours.

Discussion

Carr and his associates[23] have demonstrated that premedication with probenecid increased the concentration of free PAS in the serum of guinea pigs given sodium PAS. They found that the tuberculostatic effect of PAS in experimental tuberculosis was potentiated by the concurrent administration of probenecid. Guinea pigs given sodium PAS with probenecid manifested less active disease, an increased incidence of healing, greater regression and limitation of the disease than those treated with sodium PAS alone. The authors observed that the *in vitro* tuberculostatic potency of the serum was directly proportional to its PAS concentration. The clinical implications of these observations indicate that the therapeutic efficacy of PAS is enhanced in the presence of high and sustained PAS blood levels.

Paraff et al[24] and Favez et al[25] administered PAS intravenously daily for several weeks in the treatment of cases with acute exudative and caseous

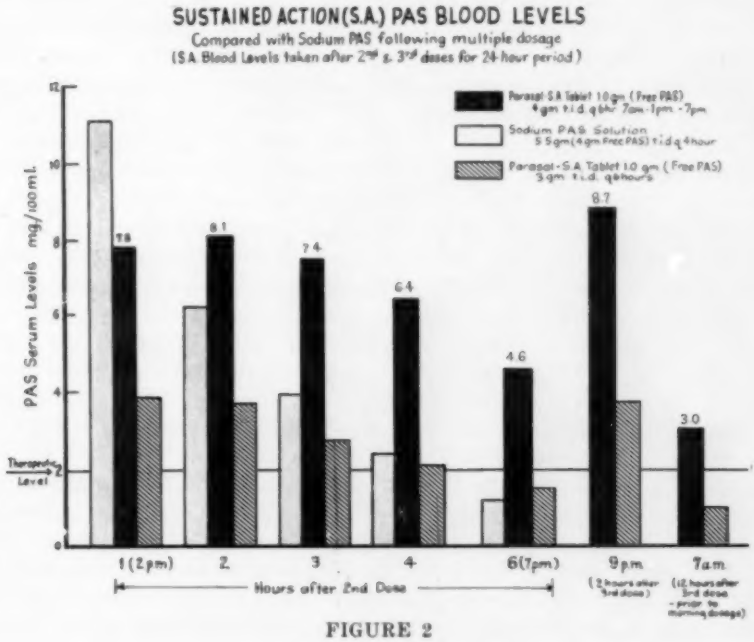

FIGURE 2

disease. They observed more rapid resolution of the disease in contrast to oral PAS therapy. They attributed the increased beneficial effects of intravenous PAS to its higher blood concentration and its greater penetration into the tuberculous lesions. In addition, Favez et al[25] claimed that the high PAS levels caused the release of ACTH from the pituitary, which in turn, exerted an anti-inflammatory effect. They indicated that the increased therapeutic response obtained in the presence of high PAS blood levels was due to its ACTH or cortisone-like action.

Hughes et al[26] and Carlson et al[27] have found a considerable increase in emergence of streptomycin resistant bacilli when streptomycin and PAS were both administered intermittently—every two or three days rather than daily. These authors emphasized that daily PAS must be given for optimum therapeutic effect as well as for the maximum inhibition of the emergence of streptomycin resistant bacilli. Studies of the British Medical Research Council[28] clearly showed that the larger the daily dose of PAS, the more effective was the protection against the development of streptomycin resistant organisms.

Heller et al[29] utilized C^{14} carboxyl labeled PAS in their studies of the metabolism of this drug both in the guinea pig and in man. They observed that the concentration of C^{14} PAS in tuberculous lesions was directly proportional to the blood PAS concentration. They emphasized that PAS like isoniazid penetrates the caseous lesions, but in contrast to isoniazid, PAS disappears from these lesions as rapidly as it does from the blood stream. This phenomenon may explain the rapid appearance of isoniazid resistant organisms when this drug is administered alone and the inhibition or delay in the emergence of such organisms when isoniazid is given concurrently with PAS. Furthermore, the potentiality of combined therapy to delay the emergence of resistant bacilli depends on the maintenance of effective PAS as well as isoniazid tissue levels, which in the case of PAS is in direct relation to its blood concentration. The significance of sustained therapeutically effective PAS blood concentrations to maintain satisfactory PAS tissue levels is, therefore, apparent.

Short[30] has demonstrated that PAS when given with sulphetrone produced an increased sulphone blood concentration. Similarly, Johnson and Corte[31] found that both PAS and sulphanilamide, when administered concurrently with isoniazid, increased the blood concentration of free isoniazid. Hughes and her associates[32] have shown that isoniazid is metabolically altered in human subjects into therapeutically inactive degradation products, the principal derivative being acetylated isoniazid. The degree of metabolic inactivation of isoniazid significantly varies in different subjects, but is fairly constant in a given individual.

Mandel et al[21] and Morse et al,[20] utilizing the serum microbiologic assay method, have demonstrated that PAS administration in man generally increased the biologically active isoniazid concentration in the blood. This is attributable to the fact that PAS competes with isoniazid as a substrate for the acetylation reaction. Mandel et al[21] have indicated that a definite correlation is present between the degree of metabolic inactivation of iso-

niazid and the decreased therapeutic response to the drug. In addition, the incidence of the emergence of isoniazid resistant bacilli is in a measure related to the degree of isoniazid acetylation and inactivation.

The implications derived from the above studies assume great clinical significance in the treatment regimens of tuberculous patients. It would appear that therapeutically sustained 24 hour PAS blood levels offer the following advantages:

1. The direct anti-microbial activity of sustained PAS concentrations within the tuberculous tissues is consistently maintained throughout the entire 24 hour period; 2. The biologically active isoniazid blood and tissue concentrations are usually elevated, thereby enhancing its anti-tuberculosis activity; 3. When administered concurrently with isoniazid, sustained concentrations of PAS and free isoniazid within the tuberculous lesions should potentiate their therapeutic efficacy, and should delay or inhibit the emergence of bacilli resistant to these drugs.

Standard PAS preparations such as sodium, potassium, calcium salts, buffered and resin PAS forms, when administered in doses of 4 gms. (free PAS), three times daily at four hour intervals, do not produce therapeutically sustained blood concentrations for the entire 24 hours. It has been demonstrated that approximately five hours after the last evening dose of sodium PAS, the most commonly used PAS preparation, the serum PAS falls below the therapeutic level.[33, 34] It is, therefore, apparent that during this interval the concentration of PAS within the tuberculous tissues is also inadequate. Thus, much of the additive therapeutic effect of PAS when administered with isoniazid or streptomycin in combined treatment regimens is lost, and the probability of the emergence of resistant bacilli is increased. In contrast, sustained action PAS tablets when administered in dosage of 4 grams three times daily at six hour intervals, provides 24 hour therapeutically effective PAS blood levels. It is emphasized that the sustained action tablets should be administered at intervals of six hours rather than the customary four hours to gain the full benefit of this medication.

PAS is relatively unstable. It readily decomposes in solution, principally into meta-aminophenol and a residue of other degradation products. Some investigators[5] believe that these degradation products may be responsible for the gastrointestinal irritation. Mitchell et al[35] attributed these adverse symptoms to PAS degradation products other than meta-aminophenol. While the causes for the gastrointestinal disturbances are not clearly established, it is significant that sustained action PAS tablets produced minimal, if any, gastrointestinal side effects in patients previously intolerant to other PAS preparations.

Sustained action PAS tablets are sodium and potassium free and are, therefore, particularly suitable for the treatment of tuberculous patients with associated cardiovascular-renal diseases. This is significant in the treatment of patients of the older age group. These patients, not uncommonly, manifest concomitant diseases which may require the restriction of sodium or potassium intake.

SUMMARY

1. Sustained action PAS tablets (Parasal-S.A., 1.0 Gm., sodium free) offer a convenient means of PAS therapy with a high degree of toleration. Acceptance of this drug was excellent since a four gram dose of free PAS consisted of only four tablets. Patients who manifested symptoms of gastrointestinal irritation due to standard PAS preparations tolerated sustained action PAS tablets with minimal, if any, gastrointestinal side-effects.

2. Sustained action PAS tablets, in dosage of four grams (4 tablets) three times daily at six hour intervals, generally provided sustained therapeutically effective PAS blood concentrations for 24 hours. No other PAS preparation, in equivalent dosage, studied to date, produced such sustained 24 hour PAS blood levels.

3. The clinical implications and probable advantages inherent in the use of sustained action PAS, administered concurrently with isoniazid or streptomycin, are believed to be as follows: a) sustained PAS concentrations within the tuberculous lesions; b) sustained and increased biologically active isoniazid levels in the blood and diseased tissues; c) greater inhibition or delay in the emergence of isoniazid or streptomycin resistant bacilli. Sustained action PAS may, therefore, serve to potentiate the therapeutic efficacy of antituberculous combined chemotherapy regimens.

RESUMEN

1. La acción sostenida de tabletas de PAS (Parasal-S.A.-, 1 grm.) ofrece un medio de la terapia por el PAS con alto grado de tolerancia. La aceptación de esta droga fué excelente, puesto de una dosis de cuatro gramos de PAS libre, consistió de sólo cuatro tabletas. Los enfermos que manifestaron síntomas de irritación gastrintestinal debida a las preparaciones comunes de PAS, toleraron.

2. Las tabletas de PAS de "acción sostenida" a la dosis de (4 tabletas) cuatro gramos, tres veces al día con intervalos de seis horas, generalmente proporcionaron un efecto mantenido consistenteen concentraciones efectivas de PAS sanguíneo por 24 horas. Ninguna otra preparación de PAS en dosificación equivalente estudiadahasta ahora, produjo niveles sostenidos en la sangre, de PAS en 24 horas.

3. Se cree que las ventajas clínicas probables resultantes deluso de PAS de acción sostenida administrado en combinación con isoniacida o estreptomicina son: a) Concentraciones sostenidas dentro de las lesiones tuberculosas; b) niveles sostenidos y aumentados biológicamente activos, de isoniacida en la sangre y en los tejidos enfermos; c) mayor inhibición o retardo en la emergencia de bacilos isoniacido o estreptomicino-resistentes.

La acción sostenida del PAS puede por tanto, servir para potenciar el efecto terapéutico de los regímenes antituberculosos combinados.

RESUME

1. Les comprimés de P.A.S. retard (Parasal, produit non sodé) offrent un moyen d'utiliser le P.A.S. avec un degré de tolérance élevé. La tolérance de cette médication est excellente depuis que la dose de 4 grammes de P.A.S. libre est administrée à l'aide de quatre comprimés seulement. Les malades

qui présentaient des symptômes d'irritation gastrointestinale imputable aux préparations habituelles de P.A.S. supportent les comprimés de P.A.S. retard avec peu ou pas de signes d'intolérance.

2. Les comprimés de P.A.S. retard dosés à 4 grammes (enquatre comprimés) donnés trois fois par jour à six heures d'intervalle, permirent généralement les concentrations sanguines de P.A.S. thérapeutiquement efficaces pour 24 heures.

3. Les conditions cliniques, et les avantages probables qui sont liés à l'utilisation du P.A.S. retard associé à l'isoniazide ou à la streptomycine sont vraisemblablement les suivants: a) une concentration de P.A.S. prolongée à l'intérieur même des lésions tuberculeuses; b) une action continue et croissante dans son activité biologique du taux de l'isoniazide dans le milieu sanguin et dans les tissus atteints; c) une possibilité plus grande de supprimer ou de retarder l'apparition de bacilles isoniazido- ou streptomycino-résistants.

Ce sont toutes ces raisons qui permettent d'obtenir avec le P.A.S. retard une plus grande efficacité thérapeutique de la chimiothérapie antituberculeuse combinée.

ZUSAMMENFASSUNG

1. PAS-Tabletten von erhöhter Wirksamkeit (Parasal-S.A., 1,0 freies Natrium ermöglichen einen günstigen Weg der PAS-Therapie mit einem hohen Grad der Verträglichkeit. Die Aufnahme, die dieses Mittel erfuhr war ausgezeichnet, nachdem eine Dosis von 4,0 freier PAS aus nur 4 Tabletten bestand. Patienten, bei denen Symptome einer Reizung des Magen-Darmkanales in Erscheinung traten infolge der üblichen PAS-Präparate, vertrugen PAS-Tabletten von erhöhter Wirksamkeit mit minimalen wenn überhaupt irgendwelchen gastrointestinalen Nebenwirkungen.

2. PAS-Tabletten mit erhöhter Wirksamkeit in einer Dosierung von 4 g (4 Tabletten) 3-mal täglich in Abständen von 6 Stunden, bewirkten im allgemeinen erhöhte therapeutisch wirksame PAS-Konzentration im Blut während 24 Stunden. Keine anderen gegenwärtig untersuchten PAS-Präparate führten in aequivalenter Dosis zu derart erhöhten 24 Stunden-PAS-Blutspiegel.

3. Die klinischen Folgerungen und die wahrscheinlichen Vorzüge, die in dem Gebrauch von PAS mit erhöhter Wirksamkeit liegen bei gleichzeitiger Verwendung mit INH oder Streptomycin, werden wie folgt angenommen: a) erhöhte PAS-Konzentration im Inneren der tuberkulösen Herde; b) erhöhte und vermehrte biologisch aktive INH-Spiegel im Blut un den erkrankten Geweben; c) grössere Hemmung oder Verzögerung im Auftreten von gegen INH oder Streptomycin resistenten Bazillen. PAS mit erhöhter Wirksamkeit kann daher dazu dienen, die therapeutische Wirksamkeit von antituberkulöser kombinierter Chemotherpeutischer Behandlungsweise zu pontenzieren.

ALL REFERENCES WILL APPEAR IN REPRINTS

The author is grateful to Mr. Martin Sass and Mrs. Vera F. Levine of the Brooklyn Veterans Administration Hospital, Medical Service, Research Laboratory for their invaluable aid in the determination of the PAS blood levels.

Glycogen Storage Disease of the Myocardium*

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Glycogen storage disease of the myocardium is a rarely observed and reported state. This is emphasized by the report of di Sant'Agnese et al.,[10] who in a review of the literature, found a total of 14 cases up to 1950. Two of these 14 cases were his own, previously reported.[3] It was also of interest to note his observation that only two cases had been found at Babies Hospital in New York in a period encompassing 27 years and 2,000 autopsies.[10] Therefore it was deemed worthwhile to add another case to the small number already present in the literature.

Case Report

J. F., a six month old white boy, was admitted to Ancker Hospital May 10, 1956 in a critical state, from another hospital where he had been hospitalized from April 17 to time of present admission. "Heavy breathing" had been present since birth, although general development and appearance were satisfactory. At three months of age, a transitory episode of cyanosis had been noted by the mother. Fever, cough, malaise had been noted at four months of age and a diagnosis of pneumonia was made. A total period of 28 days hospitalization followed, during which time antibiotic and oxygen therapy were given. Several days following discharge from the hospital, cyanosis, fever, cough, poor feeding, and excessive mucus discharge were noted. Re-hospitalization occurred April 17 and continuous oxygen therapy by means of a tent was instituted. Collapse of left lung, enlarged heart and systolic murmur were present.

Information from mother revealed that the gestation period had been normal. The birth weight was 7 pounds, 14 ounces. Poor strength had been noted from birth, in that he had been unable to hold his head up, or reach for toys, and had never used his legs. Physical examination revealed a listless, unresponsive, white infant boy who appeared to be normally developed. The state of nourishment appeared to be adequate and circumoral cyanosis was noted. Dullness on percussion was noted over the left chest in the postero-lateral aspect with decreased to absent breath sounds in this region. Breath sounds on the right were clear. Rhonchi were heard anteriorly over both lungs. The cardiac border on the left was percussed to the anterior axillary line with a heaving precordial thrust being noted. A grade II systolic murmur was noted along the left sternal body in the fourth intercostal space with a grade IV systolic murmur heard over the base in the region of the pulmonic area. The liver was palpable two finger breadths below the right costal border. Remainder of the examination was nonrevealing. Laboratory findings were as follows:

The white blood cell count was 20,400, 63 per cent neutrophils, 30 per cent lymphocytes, 6 per cent monocytes, and 1 per cent eosinophils. The electrocardiogram was abnormal with nonspecific ST and T wave changes in Lead I, AVL, V1, and V2. Posteroanterior x-ray film of chest (Fig. 1) was featured by marked cardiac enlargement, with a globular configuration. Urinalysis was negative for albumin, sugar, and showed only an occasional cast and leukocyte. Blood chemistry studies were not done at time of admission and he expired before such evaluation could be made.

Course in hospital: Marked listlessness and weakness were prominent. Feeding was inadequate because of poor sucking ability and rapid onset of exhaustion after only a short period. Lethargy and weakness increased. A weak cry was noted and a deepening cyanosis became evident. Gavage was necessary for feeding. Repeated suctioning of the oro-pharynx was necessary because of the severe degree of mucus production. He expired at 11:42 p.m. May 12.

Pertinent autopsy findings are as follows: Thorax: Right lung showed areas of atelectasis in the apical region of the upper and middle lobes, and posterior portion of the lower lobe. The left lung was completely collapsed except for a small portion of the upper lobe. Pleural spaces were negative as was the pericardial sac. Heart meas-

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ured 8 cm. in its transverse diameter and weighed 174 grams. Vessels and valves were normal in appearance. The wall of the left ventricle was markedly hypertrophied and measured 2 cm. in thickness (Fig. 2). The myocardium was pale and firm, and no evidence of sub-endocardial or myocardial fibrosis was evident.

The liver weighed 383 grams with a smooth, glistening cut surface. Spleen was normal in appearance and weighed 21 grams. The kidneys were dark red on cut section with distinct markings and normal cortico-medullary ratios. The weight of each was 24 grams.

Microscopics: See Figures 3-6.

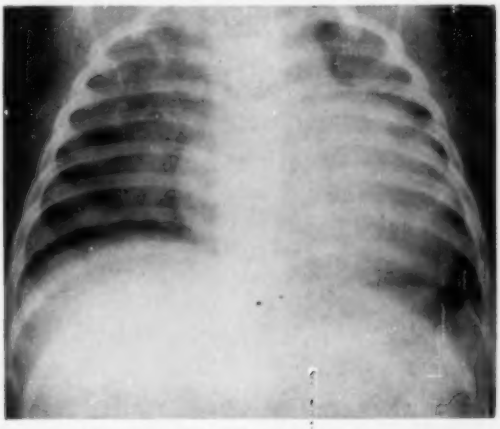

FIGURE 1: PA film of chest shows a markedly enlarged heart which has a globular appearance and "shouldering" effect most evident along the left border. The hilar vessels appear accentuated on the right with a patchy area of infiltration noted in the left apex. The secondary compressive effects of the cardiomegaly upon the left lung may be ascertained from this film.

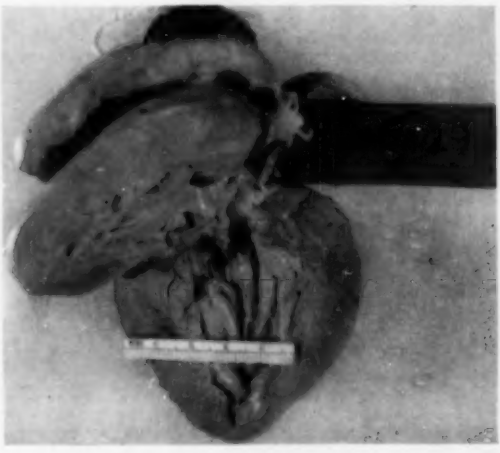

FIGURE 2: The left ventricle is sectioned across so as to reveal the marked hypertrophy of the myocardium of this chamber. The prominent hypertrophy of the columnae carnae and papillary muscles is readily discernible.

Review of the Literature

Glycogen storage disorders are of infrequent occurrence, and relatively few cases have been reported in the literature[12] to date from the time of Von Gierke's[1] description in 1929 of the autopsy findings in two cases. He called the disorder, "Hepato-nephromegalia Glycogenica." Subsequently the case reports and investigations of others[1, 7, 10, 11, 12, 22] made it apparent that this metabolic disorder as described by Von Gierke was not a sole entity, but actually one variant of an overall complex defection of carbohydrate metabolism that is featured by an abnormal glycogen storage in the body tissues and the occurrence of the disease in siblings. At

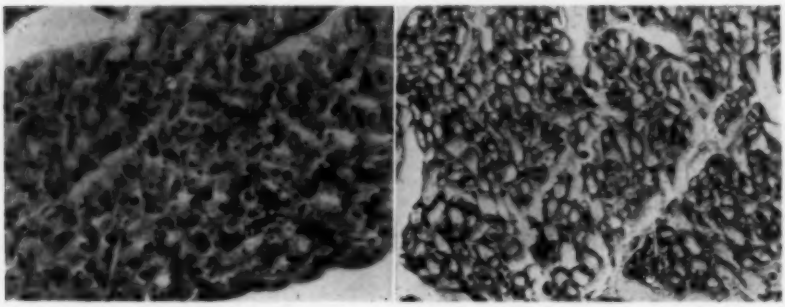

FIGURE 3A FIGURE 3B

Figure 3A: Heart. Best's Carmine Stain—The large and small punctate black granularities seen throughout the syncytium of myocardial fibers represent glycogen vacuoles which have thus become apparent because of the affinity of the glycogen for this stain.—*Figure 3B:* Heart. H & E Stain—section shows a marked vacuolated appearance of the myocardial fibers, imparting to it a "lattice work" arrangement. The nucleii are displaced laterally and may be seen at the periphery of the cell margin in some areas. The large vacuoles represent stored glycogen.

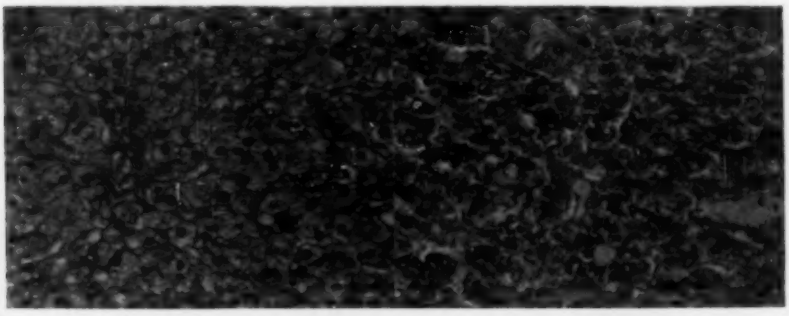

FIGURE 4A FIGURE 4B

Figure 4A: Liver (H & E Stain). Some distention of the hepatic cells is apparent with a discrete vacuolization of the cytoplasm evident. The nucleii occupy a somewhat lateral position in this section, not as prominent as seen in Figure 5A.—*Figure 4B:* Liver. Best's Carmine Stain—The finely dispersed granules seen throughout this section are within the cytoplasm of the cells and represent the sites of the small discrete glycogen vacuoles seen in Figure 4A.

the present time, five sub-divisions or variants of glycogen storage disease have been classified.[8, 10, 12] These are as follows:

(1) Hepatic (Von Gierke's Disease): This is featured by fasting hypoglycemia, acetonuria, decreased glycogen response to epinephrine and glucagon, and a prolonged glucose tolerance curve. Symptoms are chiefly

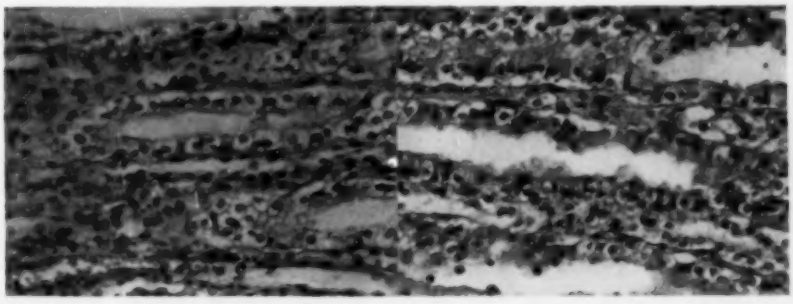

FIGURE 5A FIGURE 5B

Figure 5A: Kidney. (H & E Stain)—In this section a portion of the tubular collecting system is seen. The lining epithelial cells are noticeable by the clear vacuolated cytoplasm imparting a "ballooned" appearance to the cell. Although not prominent the nucleii occupy an eccentric position.—*Figure 5B:* Kidney. Best's Carmine Stain—Although some vacuolated epithelial cells lining the collecting tubules are still present, the discrete granularity within the cytoplasm of the majority of the other cells gives adequate evidence as to the abundance of intracellular glycogen present throughout.

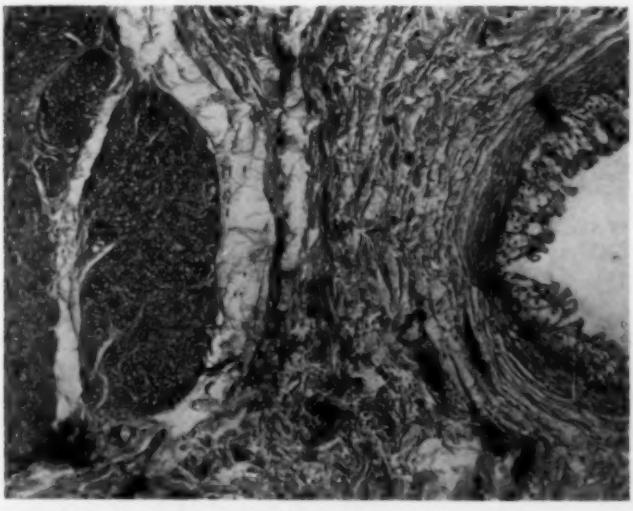

FIGURE 6: Bladder. (H & E Stain). In the superior aspect of this section the easily discernible clear "balloon like" cytoplasm of the lining transitional cells of the mucosa are apparent. In the inferior aspect a marked vacuolated or "lattice work" appearance is noted of the smooth muscle fibers. It is apparent that extensive glycogen storage is present in both sites. Even at this low power the appearance of the smooth muscle fibers is strikingly similar to that seen of the myocardium.

anorexia, disturbances of weight gain, apathy, convulsive disorders related to the hypoglycemia and coma. Physical findings are characterized by hepatomegaly, stunted growth, and occasionally palpable kidneys.

(2) Hepatic with cirrhosis—Described as a variant of the hepatic type. Hepato-splenomegaly, ascites, absence of hypoglycemia and acidosis and normal glucose tolerance curves are characteristics. Involvement of the R-E system is prominent in contrast to the hepatic type. It is conjectural as to the possibility of this representing a mild stage of the hepatic type, with the glycogen acting as a foreign body and stimulating fibrosis.[12]

(3) Hepatic and muscle—This entity is rare, with only one case[22] having been reported to date, with note of an additional case by Recant.[12] Hepatomegaly, mild hypoglycemia and acetonuria with mild normochronic anemia were noted. Follow-up to present age of 13 has revealed normal development and persistence of fasting ketonuria. Liver studies show persistent dysfunction. However, a gradual rise in the fasting blood sugar has been noted over the follow-up period.

(4) The muscular type—This also is a rarely noted variant, with four cases having been reported to date.[17] The characteristics as described have been a progressive muscular weakness simulating amyotonia congenita. The glycogen deposits are found principally in striated muscle, with some being noted also in the heart, liver, kidney, etc. In this variant the muscle glycogen was found to consist of a shorter chain length than normal and ultra centrifugal studies revealed an abnormal physical state.[14, 18]

(5) The Cardiac type—The first instance of this variant being recognized as a definite disease entity was by Pompe[16] in 1936 as a result of histo-chemical studies on a case of idiopathic hypertrophy of the heart. He described the disease as "cardiomegalia glycogenia." [11, 16] It is pertinent to remark that in his case, glycogen was found in liver, kidney, thyroid, spleen, and striated muscle. This careful delineation by Pompe served to differentiate this from "Von Gierke's disease" as recognized, and to establish a new variant. This was important in that idiopathic hypertrophy of the heart was formerly thought to be secondary to diffuse rhabdomyomata of the heart as postulated by Virchow.[11] Sub-endocardial fibroelastosis, acute interstitial myocarditis (Fiedlers myocarditis), aberrant origin of the left coronary artery from the pulmonary artery, etc., are other conditions which have been found to be causative agents of cardiac hypertrophy in infants.[10, 11] A congenital type of "idiopathic hypertrophy of the heart" was reported by Sprague[9] et al., in 1931. The description of the microscopic sections of the myocardium would lend itself quite well to a diagnosis of glycogen storage disease of the myocardium. Finkelstein,[19] in 1939, introduced the term "cardiomegalia glycogenica circumscripto," as a result of studies on a case reported in 1924 by Carrington and Krumbhaar,[20] titled "So called idiopathic hypertrophy in infancy." The patient had died at age of one year, and autopsy findings revealed that the left coronary artery originated from the pulmonary artery and a somewhat localized area of fibrosis had been noted in the myocardium. Stained sections were positive for glycogen. This finding of glycogen in

the myocardium in a localized manner may be also observed in instances of congenital heart disease[11] and sub-endocardial fibro-elastosis.[10] These cases however do not represent instances of glycogen storage disease. In this respect single or multiple tumors of the myocardium (rhabdomyomata) would also have to be considered, since positive reaction to glycogen stains are obtained in these instances.[13] The diffuse type of rhabdomyomatosis has now been clearly delineated as being glycogen storage disease of the myocardium.[10] The multiple nodular type of rhabdomyomata are frequently associated with hamartoma of the kidneys and tuberous sclerosis.[12]

The clinical aspects of glycogen storage disease of the myocardium are quite distinctive and thus permit easy separation from the other variants, The characteristic symptoms and physical findings are related to the heart and secondarily to the lungs. There is infrequently any hepatomegaly, and this, when it occurs, is only slight. Palpable spleen and kidneys are not present. The x-ray findings of a markedly enlarged heart with a globular configuration has probably been the most prominent finding.[10] This is not distinctive in itself and may be simulated by different forms of congenital cardiac lesions. The variability of murmurs on auscultation has been noted, but the predominance of systolic murmurs is characteristic. The mechanical effects of such marked cardiac enlargement are reflected as compressive and atelectatic changes of the lungs. Heavy breathing, dyspnea on exertion, with or without cyanosis, are not infrequent observations. Cardiac failure is a common mode of exodus.

Although chemistry studies were not feasible in our patient because of the unresponsive terminal state in which he entered the hospital, the observations of others[3, 8, 10, 12] are interesting in this light. DiSant'Agnese,[10] in a review of the literature and in a separate report of two cases,[3] has noted that glycosuria and acetonuria are absent. Fasting blood sugar, glucose tolerance curves, blood lactate levels, blood sugar response to injection of epinephrine and serum lipids were all within normal limits.

The electrocardiogram patterns in general have shown low takeoff and depression of the ST segments with varying changes in the T waves from inversion to diphasic appearances.[10] In our case depressed ST segments and diphasic T waves were noted in I and AVL. Elevated ST segments and diphasic T waves were noted in V1 and V2. In general inverted T waves and alterations of the ST segments with low voltage is a pattern observed in infants with origin of the left coronary artery from the pulmonary artery. This pattern, however, without the low voltage is also suggestive of glycogen storage disease of the myocardium.[10]

Discussion

The disorders of glycogen metabolism have one fundamental characteristic in common. That is, glycogen stored in the various tissues of the body becomes unavailable for metabolic needs in the form of glucose. The normal mechanisms of carbohydrate metabolism are illustrated in the following diagram[12] (Fig. 7). It is apparent that glucose taken into

the body is acted upon by ATP and hexokinase factors which converts it into glucose 6-phosphate. This in turn is acted on by phospho gluco mutase with formation of glucose-1-phosphate. Through the action of phosphorylase and the brancher enzyme, glycogen is formed with inorganic phosphate being split off in the process. The reverse process or breakdown of this stored glycogen in the liver to the glucose 1-phosphate stage involves phosphorylase plus the debrancher enzyme. Phospho gluco mutase action results in glucose-6-phosphate formation, and this latter is converted to available glucose for metabolic needs through the specific action of glucose-6-phosphatase. This enzyme is found normally in liver and kidney tissue, but not in muscle. The metabolic pathways of the other sugars are as indicated.

The disturbances of glycogen storage led to investigative procedures by Illingworth,[5,6] C. F. Cori,[15] Larner,[4,5] and G. T. Cori.[5,6] Enzymatic processes were utilized. The glycogen molecule was found to have a "tree like" structure[12] (Fig. 8) consisting of numerous inner and outer branches, the basic substance being glucose units linked in the 1-4 carbon position with the branches forming a 1-6 carbon linkage.[5] The build up of these branches requires phosphorylase and the branching enzyme. Degradation involves enzymatic action of phosphorylase and the de-

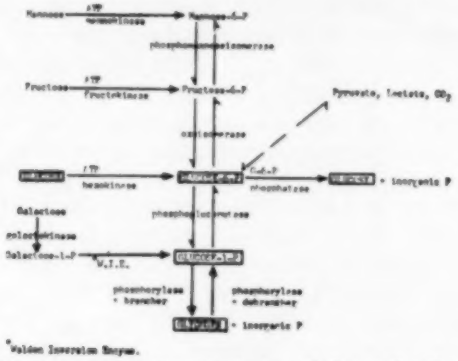

FIGURE 7: (Reprinted with the permission of the author[12] and publisher).

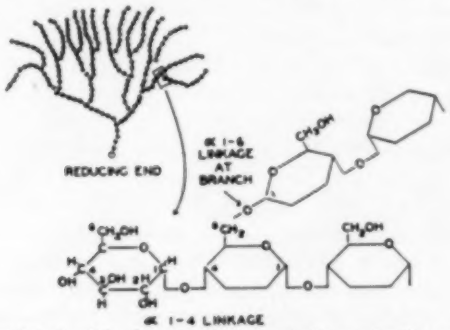

FIGURE 8: (Reprinted with the permission of the author[12] and the publisher).

brancher enzyme.[4] Thus the glucose units in the 1-4 linkage are removed singly by phosphorylase in the presence of inorganic phosphate as glucose 1-phosphate. This continues until a 1-6 linkage is encountered at which point further progress is stopped unless amylo 1-6 glucosidase, through hydrolytic action splits off the 1-6 linked residue. The process then repeats itself through these successive steps.

Larner[4] contributed further information by studying the action of branching enzymes utilizing C^{14} labeled glucose units. His study showed that phosphorylase, according to its action, governs the length of the 1-4 linked chains. The amylo 1-6 glucosidase acts on the exposed branch points (1-6 linkage) so that free glucose is split off. However, when phosphorylase acts in a formative manner, resulting in a certain number of chain lengths, the branching enzyme will act to form a 1-6 linkage from a 1-4 linkage. Larner[4] felt that this enzyme acts as a transglucosidase and called it amylo (1-4 to 1-6) transglucosidase.

The results of the above investigations indicated that the basic mechanisms underlying the variants of the glycogen storage disorders would reside in abnormalities of the structural formation of the glycogen molecule.[6, 7] This would imply aberrations within the enzymatic systems as postulated by Illingworth and G. I. Cori,[6] G. T. Cori and C. F. Cori.[7] The structural make-up of the glycogen molecule and the enzymatic system were investigated by these authors[7] in cases of the hepatic variant (Von Gierke's disease). The glycogen molecule was found to be structurally within normal limits.[6] However, complete absence to varying low levels of glucose-6-phosphatase were found to be present and the varying degree of clinical severity of the disease was thought to be directly correlated to the amount of glucose-6-phosphatase present.[7] The abnormal accumulation of glycogen in skeletal or cardiac muscle cannot be explained on variances in amounts of glucose-6-phosphatase, since this enzyme is normally absent from these tissues.

Structural analysis of glycogen in cases of the hepatic type with cirrhosis has shown fewer branch points in the molecule and a probable deficiency of the branching enzyme.[23]

In cases of the hepatic muscle variant,[12] studies have revealed shortened outer branches and probable deficiency of the debranching enzyme with intact phosphorylase.

Evaluation of the glycogen structure in cases of the muscle variant has revealed a shorter chain length[15] and an abnormal physical state on ultra centrifugation.[14]

Unfortunately, to date, little is known of the basic mechanism responsible for the cardiac variant. The glycogen content of the heart is increased to 3-10 per cent whereas the normal figure is about 1 per cent.[8] The Cori's[12] in one case found normal glycogen structure in the liver.

SUMMARY

1. A case of glycogen storage disease of the myocardium is presented with additional evidence of hepatic, renal and bladder involvement. The clinical course and autopsy findings are described.

2. The glycogen storage diseases are now recognized as being manifestations of abnormal metabolism of glycogen. There are particular chemical variations in structure as well as disturbances in enzymatic function which aid in the recognition of the particular clinical variant.

3. To date five clinical variants are recognized, each having specific clinical and laboratory features.

RESUMEN

1. Se presenta un caso de la enfermedad del glicógeno accumulado en el miocardio con compromiso adicional del hígado, riñon y vejiga.

2. Se reconoce actualmente que las enfermedades por cúmulo de glicógeno corresponden a un metabolismo anormal del glicogéno.

Hay variantes químicos particulares en la estructura así como trastornos en la función enzimática que ayudan al reconocimiento de la variante clínica en particular.

3. Hasta ahora, se han reconocido cinco variantes clínicas, cada una de ellas con características específicas clínicas y de laboratorio.

RESUME

1. Les auteurs présentent un cas d'atteinte du myocarde avec surcharge glycogénique associée à une atteinte hépatique, rénale, et vésicale. Ils en décrivent l'évolution clinique et les constatations d'autopsie.

2. Les affections avec rétention de glycogène sont maintenant considérées comme des manifestations d'un métabolisme anormal du glycogène. Ce sont des variations chimiques particulières ainsi que des troubles de la fonction enzymatique qui permettent de reconnaitre les différentes variantes cliniques.

3. Jusqu'à ce jour, cinq variantes cliniques sont reconnues, chacune ayant des caractéristiques spécifiques, cliniques et biologiques.

ZUSAMMENFASSUNG

1. Bericht über einen Fall von Glycogen-Speichkerkrankheit des Myocards mit zusätzlichen Befunden einer Beteiligung von Leber, Niere und Blase. Beschreibung des klinischen Verlaufes und der Sektionsbefunde.

2. Die Glycogen-Speicherkrankheiten werden jetzt als Manifestation eines abnormalen Glycogen-Stoffwechsels angesehen. Es sind besonders chemische Strukturveränderungen ebenso wie Störungen der enzymatischen Funktion, die dazu beitragen, bie besonders klinische Variante zu erkennen.

3. Im gegenwärtigen Zeitpunkt sind 5 klinische Varianten bekannt, von denen jede spezielle und laboratoriumsmässige Merkmale aufweist.

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Extraperiosteal Polystan Plombage: Three to Five Years' Follow-up

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Modern plombage treatment of pulmonary tuberculosis may be considered superior to the now obsolete paraffin pack operation. Three factors have contributed to improved results: (1) specific antituberculous drugs and antibiotics against pyogenic infection, (2) inert plastics as plombage material, and (3) plombage of the extra-periosteal rather than extraplural space.

Thus far, follow-up studies have not been adequate to warrant a final evaluation of modern plombage. It has not yet been proved that the modern plombage is better than older procedures. We cannot definitely answer this question because our series is too small and the period of observation is still too short. However, these cases have been followed for a longer time than those of previously published series.

In this paper, a study is presented, of 65 consecutive cases of extraperiosteal Polystan® plombage followed up for three to five years.

All cases were treated with streptomycin (or dihydrostreptomycin) and PAS. Isoniazide was not used at that time. The surgical technique employed for making the extraperiosteal pneumonolysis is that described by Bailey[16] in 1942. The Polystan® sponge used in the first third of the series was the original, rather soft type ("S"). Later the firmer "D" type was chosen as more suitable for the extraperiosteal space.

The present analysis includes all cases operated upon during the first 24 months since extraperiosteal Polystan® plombage was adopted in November 1950 as a collapse procedure for pulmonary tuberculosis. Excluded are a few cases of plombage for pleural empyema or as space-reducing measure following pulmonary resection. The intrapleural application of the Polystan® sponge following pneumonectomy shall not be dealt with in this paper.[11]

Material

Sixty-five cases of severe pulmonary tuberculosis were treated at the Municipal Chest Hospital of Copenhagen with extraperiosteal Polystan® plombage between November 1, 1950 and October 31, 1952. These cases represent our earliest experience with this technique of surgical intervention. The total number of surgically-treated cases of pulmonary tuberculosis in the same two-year period was about 700. Thus, plombage was resorted to in less than 10 per cent of the cases and, as a rule, in otherwise inoperable patients. Severe bilateral lesions and badly impaired respiratory function were the principal indications for plombage.

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Twenty-seven of the plombage patients (42 per cent) were more than 40 years of age. In the total surgical series during the same period 29 per cent were more than 40 years old.[1] Plombage was performed in 43 male and 22 female cases, whereas the sex distribution was equal in the total series.

Bilateral cavities were, at the time of surgery, present in 17 cases in the plombage series (26 per cent). Contralateral interventions were performed in 23 (35 per cent) including artificial pneumothorax in one case, traditional surgical operations in 13 and plombage in nine.

Bilateral plombage in one stage was done in three cases and in two stages in six: the interval varying from 12 days to one year. Seventy-four plombage spaces were produced in the 65 patients.

The extent of the plombages, as measured by the stripping of the ribs, was as follows: four ribs (8 cases), five ribs (22), six ribs (34), seven ribs (7), eight, nine and ten ribs (1 case each). Apicolysis was performed in 68 of the 74 plombage procedures (92 per cent). Right and left-side plombages are equally represented in the series.

In the postoperative period (two months) no breakdown or migration of the plombe, infections or other severe complications occurred. Minor complications included pleural tear during surgery (four cases), post-operative atelectasis (three cases) and wound rupture in one. In no case was it necessary to remove the plombe during the first two months following the operation.

Follow-up Analysis

All of the 65 cases, with 74 plombages, were followed until death, or up to a final examination in December 1955 and January 1956 three to five years after surgery. Thirteen deaths had occurred in this group (20 per cent), 10 from tuberculosis, three from other causes: suicide, cor pulmonale and carcinoma of the uterus; the patients had been converted for two and three years respectively. Six of the deaths had residual cavities under the plombage and four died from contralateral tuberculosis

TABLE I

CHARACTERIZATION OF THE CASES SELECTED FOR EXTRAPERIOSTEAL POLYSTAN® PLOMBAGE NOVEMBER 1, 1950-OCTOBER 31, 1952

Total number of cases		65	
Males 43, Females 22			
Age—40: 27, Age—50: 12, Age 60: 3			
Bilateral cavities		17	26 per cent
Contralateral interventions		23	35 per cent
Pneumothorax	1		
Extrapleural pneumonolysis	4		
Thoracoplasty	6		
Resection of the lung	3		
Extraperiosteal plombage	9		

without evidence of activity in the side of plombage, confirmed by post-mortem autopsy in three of the four cases.

Nine of the 65 (14 per cent) patients still living were tubercle bacillus positive. In three of these cases, a residual cavity was demonstrated beneath the plombage, while contralateral cavities were the source of the bacilli in six cases.

Forty-three of the 65 cases (66 per cent) in this study were the negative and without residual cavities. In three cases, however, the cure was attributable to secondary pulmonary resection for residual cavities under the plombage region. Conversion rate, due to the plombage itself was 62 per cent (40 cases). Repeated negative cultures obtained at least one year after cessation of antituberculous therapy was the criterion for considering a patient as converted.

Residual cavities were demonstrated in 12 cases, (16 per cent) of 74 followed-up plombage spaces. Three of these were eventually cured by resection, three were living unconverted cases, and six were fatalities. The rate of cavity closure by extraperiosteal Polystan® plombage was 84 per cent.

Bilateral plombage was performed in nine cases with five converted; two still positive and two deaths. The deaths occurred two and three years respectively after the last operation, the latter case being converted after surgery, with death due to uterine carcinoma.

Complications

No complication from the Polystan® sponge was noted in the first two months following extraperiosteal plombage.

Late complications consisted of three cases of pain referable to the plombage region. In one case the plombe was removed six months following insertion, without cessation of the complaints. It is doubtful that the pains were more pronounced than those observed in some cases of thoracoplasty. The incidence of late postoperative pains in the plombage region (5 per cent) is not different from that which was observed in a

TABLE II

CONVERSIONS THREE TO FIVE YEARS FOLLOWING EXTRAPERIOSTEAL POLYSTAN® PLOMBAGE

Total number of cases		65	
Died		13	20 per cent
Converted	3		
Contralateral activity	4		
Residual cavity	6		
Positive		9	14 per cent
Contralateral activity	6		
Residual cavity	3		
Converted		43	66 per cent
Plombage alone	40		
Plombage plus reaction	3		

follow-up of one of our thoracoplasty series,[2] in which 6 per cent complained of pain.

Inflammatory complications occurred in 11 cases (15 per cent of 75 plombage spaces): four in the first year, three in the second, two in the third, and two in the fourth following insertion of the plombe. In one case, conservative therapy cured the infection; this patient has since been followed for one and a half years and careful clinical and roentgenological observation, as well as repeated punctures have revealed no recurrence of the infection. In 10 cases the plombe was removed and thoracoplasty performed simultaneously; no postoperative mortality or complications were recorded following these interventions, nor was there reexpansion of the collapsed lungs. Two of these patients died later, one has still a small tuberculous fistula and seven are cured.

In four cases, the infections were caused by injury to plombage space as well as the pulmonary cavity during a secondary lung resection. Three of these, some of our first cases, were resected too soon after the plombage. In one case of bilateral plombage, one of the spaces was infected during the course of meningitis, probably from an old lumbar spondylitis; the pulmonary lesion itself had been arrested for more than a year. In these five cases the infection of the plombage space was tuberculous. Two of the patients are cured, one has a small fistula, and two died later. In three cases, the complication arose in plombage spaces which were filled with materials capable of inducing chemical modifications of polyethylene. In three cases non-specific infection occurred spontaneously within two, eight and 14 months following surgery; they were all cured.

Thus, seven of these instances of inflammatory complication may be attributed to artificial injuries to the plombage space and may not have

TABLE III

OPERATIVE AND POSTOPERATIVE COMPLICATIONS FOLLOWING EXTRAPERIOSTEAL POLYSTAN® PLOMBAGE

Total number of cases		65
Number of plombage spaces performed		74
Number of interventions		72
Unilateral plombage in one stage	55	
Unilateral plombage in two stages	1	
Bilateral plombage in one stage	3	
Bilateral plombage in two stages	6	
Tear in pleura		4
Atelectasis		3
Rupture of wound		1
Spreads		0
Infections		0
Mortality within two months postoperatively		0
Complications, total		8

occurred if the plombage spaces had been untouched. On the other hand four infections (one tuberculous and three non-specific), (5 per cent of 74 plombage spaces), seem to belong to an unavoidable group of post-surgical complications. All of the latter four cases were cured, three of them by surgery, one by medical measures.

Discussion

The main reason for the selection of the Polystan® sponge as plombage material is its porous, discontinuous surface. This permits ingrowth of the connective tissue into the meshes of the sponge. The plombe is so to speak "healed in" to the pneumonolysis space within a few weeks. The fixation of the plombe prevents friction against the surrounding structures. Such friction is unavoidable following insertion of plombage material with a smooth, continuous surface. Friction causes mechanical irritation—physical foreign body reaction—giving rise to effusion and the risk of infection. This is true whatever the chemical properties of the foreign body. From the experiments of Bing and Hart Hansen[3, 4] of the University of Copenhagen, it was known that the Polystan® sponge is non-absorbable and non-irritating to the tissues. It was, from a surgical point of view, considered an advantage of the Polystan® sponge, that it is non-opaque to x-rays, easy to sterilize and to modify in shape, size and consistency and finally that aspiration from and injection into the sponge itself may be performed as if it were an open space.

Morriston Davies et al.[5] had to remove five of 102 polythene packs in the early postoperative course and later 12 removals were undertaken. In our series no plombes were removed in the early postoperative period and later only three (excluding those which were artificially injured). The two series consisted of approximately the same type of cases, the surgical technique was similar and the plombage materials were chemically identical. The only apparent difference was the surface of the plombes: The polythene pack is surrounded by a film, the Polystan® sponge has a porous surface. Also, in the hands of other surgeons, in a smaller series, a striking difference in the incidence of removals between

TABLE IV

LATE COMPLICATIONS CCCURRING UNTIL THREE TO FIVE YEARS FOLLOWING EXTRAPERIOSTEAL POLYSTAN® PLOMBAGE

Number of plombage spaces		74
Pain		3- 4 per cent
Removal of plombe	1	
Inflammatory reactions and infections		11-14 per cent
Removal of plombe	10	
Causes: Injury during secondary surgery		4 —7 avoidable
Liquid paraffin	3	
Miliary tuberculosis	1	4-5 per cent unavoidable
"Spontaneous" non-specific	3	

the two types of polyethylene plombes is demonstrated (Laird and Stephens[6]).

The advantage of the extraperiosteal plombage to the extrapleural or combined types is well illustrated by the fact that the pioneers of modern plombage in Scandinavia, Linden and von Rosen[4] of the University of Lund, Sweden, who reported good initial results, later observed tuberculous space infection and bronchial fistulae in only 10 per cent of their cases.[7] They placed the Polystan® sponge partly extrapleurally, partly extraperiosteally. In a review of the literature, one of us[8] counted 39 late infections in 481 extrapleural and combined Polystan® plombages (8.1 per cent) against eight of 359 (2.2 per cent), and five of 164 (3.1 per cent), in extraperiosteal Polystan® plombage and extraperiosteal Polystan-Spongostan® plombage, respectively.

Our indications for plombage as collapse therapy in pulmonary tuberculosis were expressed in our earlier papers[9, 10, 11, 12] and have remained unchanged: "It is *not* our intention to let extraperiosteal plombage *replace* any of the old-established surgical procedures, in cases where the latter may be safely used. Plombage was considered a *supplement* to those operations which have heretofore been available in the treatment of pulmonary tuberculosis. *For the time being, plombage is, in our opinion primarily a procedure to be used when the traditional methods are considered too risky.*"[10] We still adhere to this point of view.

The results obtained in the present series cannot, of course, properly be compared with those observed in the old paraffin era, before the introduction of antibiotics and chemotherapeutics. It is illustrative of those days however, to cite some figures from the only Danish published series (Buhl[13]). Of 71 cases of extrapleural paraffin plombage, including 28 patients (39 per cent) with bilateral cavities, seven died within two months (10 per cent); 11 were cured (16 per cent); seven had rupture or late perforation of the cavity into the plombage space (10 per cent); 12 of the plombes were removed (17 per cent) and three migrated from the original space (4 per cent). A thoracoplasty series from this hospital, (1935-41) when thoracoplasty was the only surgical procedure employed, besides extrapleural pneumonolysis, and before the introduction of antituberculous drugs (Hagn-Meincke[14]) contained 2 per cent of bilaterally cavity cases; among 420 cases, 36 died post-operatively (8.6 per cent). The results after at least three years were: 46.0 per cent cured, 22.6 per cent still positive, and 31.4 per cent died (including the postoperative mortality).

The present series of 65 cases of extraperiosteal Polystan® plombage, mostly otherwise-inoperable patients, shows cavity closure in 84 per cent, and in 66 per cent conversion upon follow-up examination three to five years after surgery. (The discrepancy between the two latter figures is attributable to contralateral cavities). Inflammatory complications occurred in 15 per cent but excluding the artificially-induced instances, the complication rate was only 5 per cent. Although it is unfair to attempt to compare these data with the old Danish paraffin plombage

series, the rate of cures was one fourth of that obtained by Polystan® plombage and the number of complications several times higher.

In spite of its superiority to the extrapleural paraffin pack, the modern extraperiosteal Polystan® plombage presents certain inconveniences, especially the risk of late complications. It is uncertain whether pain is more or less serious and frequent following plombage, than following thoracoplasty. But it is evident that late infection is a constant threat to all patients bearing a plombe. Contrary to the old conception, however, infection of the plombage space today is rarely dangerous, provided correct treatment, usually the removal of the plombe, and at the same time, the over-lying ribs, thus converting the plombage to an ordinary thoracoplasty, is undertaken. Physiologically, this operation is an extrathoracic one because a firm layer of regenerated bone has formed between the plombage space and the collapsed lung. With primary closure, without drainage—even in the presence of severe infection—the space is rapidly closed during follow-up treatment, by aspiration and injection of antibiotics, according to the type and sensitivity of the infecting organisms.

A further, unknown risk of plombage, may be the possibility of development of sarcoma. Many plastics, as well as other materials, are able to induce malignant tumors in the rat. In man, however, no instance has been verified in spite of the fact that plastics have been used in surgery for 15 years. Moreover, Bing[15] points out, that Polystan® sponge is unlike extruded plastic materials of the same molecular structure inasmuch as the molded plastics which have never induced sarcoma in the rat.

The risk of late infection, although infrequent and not overly dangerous, and the theoretical risk of late development of malignancy, are in our opinion sufficient to contraindicate plombage as a routine collapse method. In most cases, a satisfactory collapse can be obtained by other surgical procedures. In cases of severely reduced respiratory capacity and in cases of extensive bilateral disease, in which no other surgical procedure will be tolerated by the patient, extraperiosteal Polystan® plombage is a logical procedure.

SUMMARY

Sixty-five cases of pulmonary tuberculosis were selected for extraperiosteal Polystan® plombage, mainly because they were considered inoperable by traditional methods. Severely impaired respiratory function and/or bilateral cavitation were the most common indications for plombage. Bilateral cavities were present in 26 per cent of these cases.

The plombages were undertaken during a two-year period (1950-52). In this period the total number of surgically-treated cases of pulmonary tuberculosis was about 700, of which plombages constituted less than 10 per cent.

Seventy-four plombages were performed in the 65 cases, nine of which were bilateral plombages. In 14 cases, other contralateral surgical interventions were employed.

No immediate or early postoperative mortalities or complications occurred.

Post-surgical follow-up of from three to five years showed cavity closure in 84 per cent of these cases. Twenty per cent had died, but half the deaths were attributable to contralateral activity or to non-tuberculous diseases. Fourteen per cent were positive, two thirds of them having closed cavities under the plombage, but contralateral activity. Of these cases, 66 per cent were converted, of which 62 per cent were attributable to plombage itself, the remainder to secondary pulmonary resection.

There was no mortality, no complications and no reexpansion of the collapsed lung following removal of the plombe and conversion of the plombage collapse to thoracoplasty. Two patients died later, one has a small fistula, seven were cured.

RESUMEN

Se escogieron 65 casos de tuberculosis pulmonar para aplicarles prombaje extraperióstico de Polistan® principalmente porque se consideraron inoperables por los métodos tradicionales. Las más comunes indicaciones fueron la insuficiencia respiratoria, y/o excavación bilateral. En 26 por ciento de estos casos existían cavidades bilaterales.

Los plombajes se llevaron a cabo en dos años (1950-52). En este período el número total de casos tratados quirúrgicamente por tuberculosis pulmonar de alrededor de 700 entre los que los plombajes fueron menos de 10 por ciento.

Setenta y cuatro plombajes se hicieron en 65 casos, siendo nueve de ellos bilaterales. En 14 casos, se hizo otra forma de intervención quirúrgica en al lado opuesto.

No hubo mortalidad postoperatoria inmediata ni complicaciones.

El seguimiento postoperatorio de tres a cinco años mostró el cierre de cavidades en el 84 por ciento de los casos. Veinte por ciento han muerto pero la mitad de las muertes puede atribuirse a actividad del positivos teniendo, los dos tercios de ellos, cavidades cerradas bajo el plombaje pero con actividad contralateral.

De estos casos, 66 por ciento viraron a negatividad, de los que 62 por ciento se atribuyen al plombaje mismo y el resto a resección pulmonar secundaria.

No hubo mortalidad, no complicaciones, ni reexpansión del pulmón colapsado al extraer el plombaje y convertirse en toracoplastía.

Dos enfermos murieron más tarde, uno tenía una pequeña fístula, y siete curaron.

RESUME

65 cas de tuberculose pulmonaire étaient sélectionnés pour plombage au Polystan®, principalement parce qu'ils étaient considérés comme inopérables par les méthodes traditionnelles. Fonction respiratoire sérieusement impaire et/ou cavitation bilatérale étaient les indications les plus communes pour plombage. Des cavités bilatérales existaient en 26% de ces cas.

Les plombages avaient lieu dans le courant d'une période de deux ans

(1950-52). Dans cette période le nombre total de cas de tuberculose pulmonaire traités chirurgicalement était d'environ 700, parmi lesquels les plombages constituaient moins de 10%.

74 plombages étaient exécutés dans les 65 cas, dont 9 étaient des plombages bilatéraux. Dans 14 cas, d'autres interventions chirurgicales contrelatérales ont été employées.

Aucune mortalité immédiate ou précocement post-opératoire, ni de complications n'ont apparu.

Des revues post-opératoires pendant une période de trois à cinq ans montraient de la clôture cavitaire dans 84% de ces cas. 20% avaient décédé, mais la moitié des décès étaient attribuables à une activité contrelatérale ou à des maladies non-tuberculeuses. 14% étaient positifs, deux tiers en accusant des cavités closes au-dessous du plombage, mais de l'activité contrelatérale. Sur l'ensemble des cas, 66% étaient convertis, dont 62% étaient attribuables au plombage lui-même, le reste à de la résection pulmonaire secondaire.

Il n'y avait pas de mortalité, ni de complications, ni de ré-expansion du poumon collabé après l'enlèvement du plomb dans 10 cas d'infection tardive et la conversion de collapsoplombage en thoracoplastie. 2 malades ont décédé plus tard, un malade accuse une petite fistule, 7 ont guéri.

ZUSAMMENFASSUNG

Für eine extraperiostale Polystan-Plombierung wurden 65 Fälle von Lungentuberkulose ausgewählt, vor allem weil sie als nach den traditionellen Methoden inoperabel galten. Schwer geschädigte Atemfunktion und/oder beidseitige Cavernisierung waren die häufigsten Indikationen zur Plombierung. Bilaterale Cavernen lagen in 26% dieser Fälle vor.

Die Plombierungen erfolgten während einer Zweijahresperiode (1950-52). In diesem Zeitraum betrug die Gesamtzahl der chirurgisch behandelten Fälle von Lungentuberkulose ungefähr 700, von denen die Plombierungen weniger als 10% ausmachten. Bei den 65 Fällen wurden 74 Plombierungen vorgenommen, von denen 9 bilaterale Plombierungen waren. Bei 14 Fällen wurden andere kontralaterale chirurgische Eingriffe angewandt.

Es ereigneten sich keine unmittelbaren oder frühen postoperativen Todesfälle oder Komplikationen. Nachuntersuchungen 3-5 Jahre nach der Operation ergaben Cavernenvernichtung in 84% dieser Fälle. 20% waren verstorben, aber die Hälfte dieser Todesfälle war auf kontralaterale Progredienz oder auf nicht tuberkulöse Erkrankungen zu beziehen. 14% waren positiv, von denen 2/3 die Cavernen unter der Plombierung verschlossen hatten, jedoch auf der Gegenseite aktiv waren. Von diesen Fällen hatten 66% ihre Bazillen verloren, wobei 62% auf die Plombierung selbst zu beziehen waren und die übrigen auf sekundäre Lungenresektion.

Es bestanden keine Mortalität und keine Komplikationen und keine Wiederausdehnung der kollapierten Lunge im Anschluss an die Plombenentfernung und die Umwandlung des Plombenkollapes zur Thorakoplastik. 2 Kranke starben später, einer hatte eine kleine Fistel und 7 wurden geheilt.

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Experimental Alteration of Pulmonary Functions

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Knowledge of the effects of experimental pulmonary disease on pulmonary function has bearing on the effects of various human diseases on pulmonary function In addition, information about reserves of pulmonary function present in normal animals and the types of functional limitation that occur under various conditions may be related to human disease. For the purpose of this review, pulmonary function will be subdivided into ventilation, diffusion and distribution of blood and gas in the lung.

Ventilatory function, of which the end result is alveolar ventilation, includes the phenomena responsible for the nervous and chemical control of respiration, the thoracic and diaphragmatic innervation and musculature, the compliance of the lung and chest, the resistance to airflow through the airways and the size of the lung dead space. *Diffusion* refers to the diffusion of oxygen from the alveoli into the blood circulating through the alveoli. The measurement of this function, the diffusing capacity of the lung, is defined as the volume of oxygen consumed by the lung per minute per mm. mercury pressure difference between the alveolar tension and the mean oxygen tension in the blood flowing through the lung capillaries. *Distribution* refers to the areas to which blood and gas flow in the lung, particularly in reference to one another. The pulmonary circulation will be considered as a component of the distribution function.

A number of methods are available for producing impairment of one or more of these functions, and the effects of various experimental diseases and procedures on these functions will be reviewed. Limitation of each of the three functions results in distinctly different physiological abnormalities.[1] *Reduction of alveolar ventilation* results in elevation of alveolar and arterial carbon dioxide tensions with comparable reductions of alveolar and arterial oxygen tensions. Because of the flat shape of the oxygen dissociation curve above an oxygen tension of 70 mm. Hg., the arterial oxygen tension has to be greatly reduced before arterial unsaturation results. However, slight elevation of the carbon dioxide tension results in acidosis until it is compensated by renal retention of bicarbonate. *Impaired diffusion* results, eventually, in anoxemia which is greatly aggravated by inspiration of a low oxygen mixture, ascent to high altitude, or by increased oxygen consumption such as occurs during muscular exercise. Because of the relatively great diffusibility of carbon dioxide, CO_2 retention would only be expected to be significant when anoxemia were present to an extent incompatible with life. *Impaired distribution* may take the form of an effective right-to-left shunt which results in anoxemia from the mixture of venous blood with blood arterialized in the lung. Carbon dioxide retention need not occur when reduction of the arterial oxygen saturation

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is present from a shunt because the venous carbon dioxide content is not as different from the arterial carbon dioxide content as the venous oxygen saturation is different from the arterial oxygen saturation. Thus, admixture of a small amount of venous blood containing 55 volumes per cent of CO_2 to pulmonary capillary blood with 51 volumes per cent of CO_2 has an inappreciable effect on the resultant arterial carbon dioxide content whereas the addition of a small amount of venous blood with an oxygen saturation of 75 per cent to pulmonary capillary blood with an oxygen saturation of 98 per cent results in detectable anoxemia. Impaired distribution may also take the form of different ventilation/perfusion ratios in different parts of the lung, in which case carbon dioxide retention does occur, but the anoxemia is more severe. Finally, reduction of the size of the circulatory bed produces impairment of right ventricular function and, as will be discussed, of diffusion in the lung.

General anesthesia. This subject has recently been reviewed by Dripps and Severinghaus.[2] The physiological effects of anesthetic agents depend largely on the type and strength of anesthetic used, but the common effect of all agents is, eventually, to reduce alveolar ventilation and, thus, to cause retention of carbon dioxide and respiratory acidosis. Additional effects of anesthetic agents include the production of bronchial constriction, pulmonary edema, decreased lung compliance and atelectasis, but the major effect is to reduce alveolar ventilation.

Pulmonary edema may be produced experimentally by means of a variety of agents.[3] Alphanaphthylthiourea (ANTU) causes pulmonary edema, apparently, by increasing the permeability of the lung capillaries to protein.[4] Pulmonary edema produced by ANTU in dogs results, early, in diminished compliance of the lung.[5] The reduction in compliance, however, is insufficient by itself to reduce alveolar ventilation. Anoxemia develops later because some blood perfuses alveoli which are not ventilated because foam and edema fluid obstruct the airways.[6] There is no apparent impairment of diffusion through the walls of ventilated alveoli.[6] Since the anoxemia is due to an effective right-to-left shunt, the administration of oxygen produces little impairment of the arterial oxygen saturation, whereas antifoaming agents or positive inspiratory pressure might be expected to result in better alveolar ventilation through foam-filled airways.

Resection of lung tissue. In acute experiments on anesthetized dogs, pneumonectomy results in a small rise of the pressure in the pulmonary artery,[7] but pulmonary hypertension only becomes severe (with development of right heart failure) after resection of some 70 per cent of the lung.[8] At this stage, ventilatory function remains adequate, and there is no apparent impairment of distribution of blood and gas in the remaining lung. However, resection of this much pulmonary tissue does cause impaired diffusion of oxygen, resulting in anoxemia which is completely relieved by oxygen. This diffusion limitation apparently results from the fact that the alveolar capillary surface area is so small that the alveolar-mean capillary oxygen tension differences must be large to permit diffusion of the required amount of oxygen from alveoli to the blood. Stated differently,

the entire cardiac output circulates at an accelerated velocity through a reduced number of capillaries so that the blood leaves the lung at an oxygen tension considerably lower than the alveolar oxygen tension. Elevation of the alveolar oxygen tension, by inspiration of oxygen, increases the pressure gradient for diffusion so that more oxygen diffuses into the blood and the anoxemia is completely overcome. Thus, in the dog, functional limitation after resection of pulmonary tissue occurs from inadequate diffusion and from restriction of the pulmonary vascular bed, resulting in right heart failure; there is no significant impairment of the ventilatory or distributive functions.

The chronic effects of pneumonectomy have been studied by Carter et al[9] who found that, in puppies, pneumonectomy resulted in no apparent impairment of exercise tolerance, as measured by ability to run on a treadmill for two hours and by the arterial oxygen saturation after the run, whereas adult dogs subjected to pneumonectomy demonstrated decreased ability to run on a treadmill and increased anoxemia after the exercise. Phillips et al, resecting pulmonary tissue in stages, found that as much as 85 per cent of the lung could be removed from adult dogs without apparent impairment of health.[10] Although microscopic examination of the tissues of these animals revealed evidence of emphysema, studies of pulmonary function were not reported. It is apparent that the pulmonary reserve is such that extensive resection of lung tissue, particularly if done in stages, can be tolerated by normal animals.

Pulmonary arterio-venous fistula. This abnormality has been created in dogs with the production of anoxemia due to right-to-left shunt of the blood through the abnormal circulatory pathway.[11] Though they were not measured, other pulmonary functions may be presumed to be unaffected by such a lesion.

Lung collapse. In 1931, Moore produced collapse of one lung in closed-chest dogs and found that, 15 to 75 minutes later, the blood flow through the collaped lung amounted to 0 to 42 per cent of the total blood flow.[12] Similar data were obtained by Andrus.[13] More recently, Peters and Roos found, in open-chest dogs, that collapse of one lung resulted in an immediate (10 min.) reduction of the blood flow to 0 to 34 per cent of the total flow due to a marked increase in pulmonary vascular resistance.[14] Further reduction of the blood flow did not occur up to three hours after collapse. Furthermore, another group of animals was allowed to survive for periods up to six months, and they showed similar reductions in flow through the permanently collapsed lung. Whether the increased vascular resistance in the collapsed lung was due to mechanical collapse or compression of blood vessels or to a neurogenic stimulus remains to be determined. Pertinent to point is the observation that inflation of the lung in dogs, either by positive pressure at the upper airway or by negative pressure around the chest, results in an increase of the pulmonary vascular resistance.[15, 16] It is possible, however, that complete collapse of the lung, not studied by the above authors, also results in increased vascular resistance due to closure of the blood vessels.

Additional data on the chronic effects of unilateral collapse of the lung has been obtained by Rosenberg,[17] who discovered that chronic collapse of one lung resulted in a reduction of blood flow through that lung and that anoxemia did not develop, even during exercise. In addition, there was no significant rise of the resting pressure in the pulmonary artery, and there was a fall of the mean intrapleural pressure on the side of the collapse.

Apparently, after acute or chronic collapse of part of the lung, anoxemia is prevented by the development of increased vascular resistance in the collapsed lung so that blood is shunted away from the non-ventilated lung. Ventilatory and diffusion limitation would be expected to develop only after collapse of over 70 per cent of the lung (see above: Resection of lung tissue).

When the lungs are allowed to collapse completely at the end of each expiration during positive pressure ventilation in the open-chest dog, anoxemia results.[18] Study of the alveolar and arterial oxygen tensions at three levels of oxygenation in these animals indicated that the anoxemia is a result of impaired distribution because of the presence of different ventilation/perfusion ratios in various parts of the lungs, rather than the result of right-to-left shunt or impairment of diffusion. Apparently normal lung architecture is important in maintaining blood and gas flows of similar magnitude to various areas of the lung. Anoxemia might be expected to occur in patients with pneumothorax and partial lung collapse and, if so, should be overcome by the administration of oxygen. In connection with the experimental or therapeutic production of pneumothorax, the theoretical analysis of Fenn[19] is of interest. Normally the intrapleural pressure is as much a result of the elasticity of the chest wall and diaphragm pulling out as to the elasticity of the lungs pulling in. The same is true when air is introduced into the pleural space, except that under these circumstances both chest and lungs approach more closely their equilibrium positions, and the negative pressure in the intrapleural space is less. If sufficient air is introduced to permit both chest and lungs to reach their equilibrium positions, the intrapleural pressure will be atmospheric. Thus, introduction of air into the pleural space will cause both collapse of the lungs and expansion of the chest cage. Because of the pressure volume characteristics of the lungs and chest, introduction of a given volume of air produces approximately half collapse of the lung and half expansion of the chest wall, so that collapse of a given volume of the lung would require the introduction of approximately twice that volume of air.

The observation by Van Allen and collaborators[20] that there is communication between the peripheral branches of the bronchial tree which permits of gas exchange has important bearing on the problem of atelectasis. Although obstruction of a first order bronchus invariably leads to atelectasis, obstruction of a bronchus beyond the second order does not always lead to atelectasis, and studies of the composition of the gas in the alveoli ventilated by collateral roots indicated approximately 10 per cent efficiency of ventilation of this area.[21] Additional investigation in Lindskog's labo-

ratory led to the discovery that histamine blocked collateral respiration and that a prior injection of an anti-histaminic agent prevented this action of histamine.[22] This observation may have bearing on the pathogenesis and prevention of postoperative atelectasis.

In 1934, Lindskog and Bradshaw demonstrated that reinflation of an atelectatic lung required pressures of from 12 to 16 centimeters of water, and that the pressure required for reinflation of this atelectatic lung did not increase with time.[23] The existence of a threshold pressure which must be reached before reinflation of an atelectatic lung can occur is of obvious clinical significance.

The observation of Radford[24] that surface tension, after lung collapse, tends to make the lung less compliant, has a bearing on the management of patients encased in a respirator. In such patients, deprived of normal cough and sighing movements, atelectasis and decreased compliance of the lungs develop so that large pressures are required to provide adequate alveolar ventilation. Furthermore, the ensuing alteration of ventilation/perfusion relationships may account for the anoxemia often found in these patients. There appears to be ample justification for the therapeutic production of occasional deep breaths in these patients by the application of either positive pressure at the mouth or of negative pressure in the respirator.

Pulmonary emboli. A number of observers have produced pulmonary emboli in various species of animals with a variety of materials during the past 50 years.[25] Sufficient embolization of the lungs eventually results in right heart failure and death, and, in the anesthetized dog, this result is attributable to obstruction of pulmonary vessels by the emboli rather than to reflex pulmonary vasoconstriction.[26, 27] In addition, when pulmonary hypertension becomes severe, diffusion limitation develops and anoxemia, relieved by oxygen, results.[26] These findings are similar to those seen after resection of pulmonary tissue, and similar hemodynamic effects have been produced by direct reduction of the pulmonary vascular bed by ligation or compression of the major pulmonary arteries. Fineberg and Wiggers[28] found that, in open-chest dogs, compression of the pulmonary artery to 60 per cent of its normal size resulted in right heart failure, attributed to mechanical obstruction to the flow of blood to the lung. Similar results were obtained by Gibbon and Churchill[29] who also found that over 70 per cent of the lobar arteries had to be ligated before right heart failure developed.

Since evidence of a neurogenic component to the pulmonary hypertension which follows pulmonary embolization is lacking and since the undesirable consequences of embolism are mechanical obstruction to blood flow through the lung and right heart failure, rational therapy should be directed at improving right ventricular function and maintaining blood flow through the lung. Adrenalin is capable of sustaining the blood pressure and cardiac output in the experimental animal[30] and in patients[31] with shock following pulmonary emboli and may be life-saving. Eventually, additional pulmonary blood vessels open and permit adequate circulation through the lung at a reduced pressure in the pulmonary artery. An in-

dication of the extensive pulmonary vascular reserve is the fact that three dogs were each given pulmonary emboli to the point of right heart failure and, two to four weeks later, the pulmonary artery pressure was normal and the same dose of glass beads was needed again to produce heart failure.[30] This sequence was repeated two more times in each animal. Given supportive therapy during the acute episode, the patient with pulmonary emboli may be expected to improve as new blood vessels open in the lung.

Bronchial collateral circulation. The existence of a bronchial collateral blood flow to the lung has been found in normal dogs,[32] but its magnitude is not considered to be of physiological importance.[33] After chronic ligation of the pulmonary artery, however, the bronchial collateral flow gradually increases, and, at the end of one year, becomes of great magnitude.[33] The expanded bronchial bed in patients with bronchiectasis and other pulmonary diseases may be a factor in the left ventricular hypertrophy which may develop in such patients.

Pulmonary emphysema. Various surgical methods have been reported as capable of producing pulmonary emphysema in dogs.[34] These methods, involving increase of the thoracic cage by rib resection or "reefing" of the diaphragm, or airway obstruction by insertion of valves into the trachea, have resulted in the pathological picture of emphysema. Paine has shown that both types of procedure result, in the dog, in abnormal pulmonary distensibility, manifested by greater intrapleural pressure swings during quiet breathing and, also, in intolerance to exercise.[35] The similarity of these experimental preparations to patients with pulmonary emphysema remains to be demonstrated.

Bronchiectasis. Although bronchiectasis has been produced in experimental animals,[36] the effects of the pathology on pulmonary function have not been studied.

Pneumoperitoneum. Beecher et al[37] found that the production of pneumoperitoneum in the anesthetized dog resulted in reduction of the functional residual capacity of the dog.

DISCUSSION AND SUMMARY

Methods for producing limitation of one or more of the three pulmonary functions have been discussed and are summarized in Table I. Inadequate

TABLE I

Pulmonary Function	Experimental Procedure
Ventilation	Depression of respiratory center by anesthesia; muscular paralysis by curare; artificial dead space
Diffusion	Resection of pulmonary tissue Pulmonary emboli
Distribution	
R-L Shunt	Pulmonary a-v fistula Pulmonary edema Atelectasis
Uneven vent.-perf.	Partial lung collapse

ventilatory function may be produced by anesthetic agents and by muscular paralysis. Reduction of alveolar ventilation in the presence of increased total ventilation may be produced by the addition of an artificial dead space. Reduction of lung compliance may be produced by experimental pulmonary edema. Impaired diffusion results from resection of pulmonary tissue and from extensive pulmonary embolization, but pulmonary fibrosis and diffusion limitation from increased thickness of the alveolar-capillary membrane has not been produced in experimental animals. Impaired distribution, in the form of different ventilation/perfusion ratios in different parts of the lung, may be produced by partial collapse of the lung, and effective right-to-left shunt of mixed venous blood may be produced by pulmonary edema or by the surgical construction of a pulmonary arteriovenous fistula. The anoxemia that might be expected to result from complete lung collapse is prevented by effective shunting of blood away from the atelectatic lung, and functional limitation would only be expected to occur when large amounts of pulmonary tissue are collapsed. The functional reserve of the lung, in terms of the circulatory bed and diffusion surface, is obviously large, and mechanisms exist to prevent the development of anoxemia due to impaired distribution under abnormal conditions. Measurements of vital capacity are impossible in the experimental animal, but, by inference from human data, ventilatory reserve is also great, and after resection of pulmonary tissue, inadequate diffusion surface and pulmonary vascular bed prove to be limiting factors before alveolar ventilation becomes inadequate.

DISCUSION Y RESUMEN

Los métodos para producir la limitación de una o más de las funciones pulmonares se discuten y se resumen en el cuadro 1. Puede producirse una función ventilatoria inadecuada por los agentes anestésicos y por la parálisis muscular. La reducción de la ventilación alveolar en presencia de un aumento de la ventilación total puede producirse por el agregado de un "espacio muerto" artificial. La reducción del rendimiento pulmonar puede ser producida por el edema pulmonar experimental. La difusión reducida resulta de la resección de tejido pulmonar y después de embolización pulmonar extensa pero la fibrosis pulmonar y la difusión limitada a causa de engrosamiento de la membrana alveolo-capilar no se ha producido en los animales de experiencia. La distribución imperfecta en la forma de relación ventilación: perfusión diferente en diversas partes del pulmón puede producirse por el colapso parcial del pulmón, y se puede producir una intercomunicación de derecha a izquierda de sangre venosa mezclada por el edema pulmonar o por el establecimiento quirúrgico de una fístula arteriovenosa pulmonary. La anoxemia que podría esperarse resultara de un colapso completo del pulmón se evita por una intercomunicación efectiva fuera del pulmón atelectásico y sólo son de esperarse limitaciones funcionales cuando grandes volúmenes de ejido pulmonar se colapsan.

La reserva funcional del pulmón en términos de lecho circulatorio y superficie de difusión es evidentemente amplia y existen mecanismos para

evitar el desarrollo de anoxemia debida a distribución imperfecta bajo condiciones anormales. Las medidas de la capacidad vital son imposibles en el animal de experiencia por inferencia de los datos en el hombre la reserva ventilatoria es también grande y después de resección de tejido pulmonar la superficie de difusión inadecuada así como del lecho vascular pulmonar demuestran ser los factores limitantes antes que la ventilación alveolar se haga deficiente.

RESUME

Les méthodes capables de réaliser une réduction d'une ou de plusieurs des trois fonctions pulmonaires sont discutées et résumées dans le tableau I. Une fonction ventilatoire insuffisante peut être produite par des agents anesthésiques et par une paralysie musculaire. La réduction de la ventilation alvéolaire, alors que la ventilation totale est augmentée, peut être produite par l'addition d'une zone morte artificielle. La réduction de la capacité pulmonaire peut être réalisée par un oedème pulmonaire expérimental. Des troubles de la diffusion surviennent après résection de tissu pulmonaire et après embolies pulmonaires extensives, mais la fibrose pulmonaire et la réduction de la diffusion provenant de l'augmentation de l'épaisseur de la membrane alvéolo-capillaire n'a pu être réalisée expérimentalement chez l'animal. Les troubles de distribution par altération des rapporte qui unissent la ventilation et la perfusion, dans différentes parties du poumon, peuvent être produits par des collapsus pulmonaires limités; un véritable shunt de droite à gauche, avec mélange de sang veineux peut être produit par l'oedème pulmonaire ou par la création chirurgicale d'une fistule pulmonaire artérioveineuse. L'anoxémie qui pourrait résulter d'un collapsus pulmonaire total est supprimée par la dérivation du sang de la partie atélectasiée, et on ne doit s'attendre à une diminution fonctionnelle que lorsque de grandes quantités de tissu pulmonaire sont collabées. La réserve fonctionnelle du poumon comprenant le lit circulatoire et la surface de diffusion, est évidemment étendue, et il existe des mécanismes qui empêchent le développement de l'anoxémie qui pourrait survenir à la suite de troubles de la distribution dus à des états pathologiques. La mesure de la capacité vitale est impossible expérimentalement chez l'animal. Toutefois, en se référant à ce qu'on constate chez l'homme, la réserve ventilatoire est également grande; après une résection de tissu pulmonaire, la réduction de la surface de diffusion et du lit vasculaire pulmonaire représentent des facteurs qui agissent avant même que la ventilation alvéolaire ne devienne insuffisante.

ZUSAMMENFASSUNG

Es wurden Methoden besprochen zur Beschaffung der Begrenzung einer oder mehrerer der 3 Lungenfunktionen, und diese sind in Tabelle I zusammengefasst. Inadaequate, ventilartorische Funktion kann zustande kommen durch Anaesthetika und durch Muskellähmung. Eine Verminderung der alveolären Ventilation beim Bestehen einer vermehrten Gesamtventilation kann entstehen durch Hinzufügung eines künstlichen Totraumes.

Eine Verminderung der Lungenleistung kann erzeugt werden durch ein

experimentelles Lungenödem. Eine Herabgesezzte Diffusion ist die Folge einer Resektion von Lungengewebe und von einer ausgedehnten Lungenembolie; aber eine pulmonale Fibrose und Einschränkung der Diffusion als Folge einer verstärkten Verdickung der alveolären Kapilar-Membran ist bei Versuchstieren nicht erzeugt worden. Eine Schädigung der Distribution in der Form voneinander abweichendev Verhältniszahlen von Ventilation zu Perfusion in verschiedenen Lungenabschnitten kann er zeugt werden durch partiellen Lungenkollaps, und ein wirksamer Rechts-Links-Shunt mit umschriebenem venösen Blut kann erzeugt werden durch ein Lungenödem oder durch die Bildung einer venösen Fistel auf chirurgischem Wege. Man verhindert die Anoxaemie, die als Folge eines kompletten Lungenkollapses vermutet werden könnte durch ausreichende Querverbindung des Blutes jeweils der atelektatischen Lunge, und eine funktionelle Einschränkung ist nur zu erwarten, wenn erhebliche Bereiche des Lungengewebes kollabiert sind. Die funktionelle Reserve der Lungen hinsichtlich der Zirkulationsverhältnisse und der Diffusion der Oberfläche ist augenscheinlich gross, und es bestehen Vorrichtungen, um die Entwicklung einer Anoxaemie als Folge geschädigter Distribution unter den abnormalen Bedingungen zu verhindern. Die Bestimmungen der Vitalkapazität lassen sich beim Versuchstier nicht durchführen. Aber von den Werten beim Menschen lässt sich rückschliessen, dass die Atemreserve ebenfalls gross ist, und es lässt sich nachweisen, dass nach der Resektion von Lungengewebe eine inadaequate Diffusions-Oberfläche und Lungenverhältnisse einschränkende Faktoren sind, noch ehe die alveoläre Ventilation unzureichend wird.

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The Role of "Positive" Auricular Biopsy in Mitral Stenosis

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Introduction

Microscopic examination of left auricular biopsy has been a routine procedure since the advent of mitral valve surgery. A "positive" auricular biopsy with the presence of so-called Aschoff lesions, presumably indicating rheumatic activity, is frequently encountered under such circumstances even in the absence of clinical or routine laboratory criteria suggestive of active rheumatic carditis.[1-8] An attempt is made in this series to objectively evaluate the results of surgery in patients with predominant mitral stenosis and "positive" auricular biopsy.

Methods and Material

Microscopic sections of left auricular biopsy were available from 81 patients who were subjected to mitral valve surgery. All microscopic slides were independently reviewed by the authors and by members of the Department of Pathology.† Sections containing Aschoff lesions were arbitrarily graded 1+ to 4+: 1+ when an occasional Aschoff lesion was present to 4+ with many of these characteristic lesions.[2] Evidence of rheumatic activity by clinical or routine laboratory criteria was sought and none was found. The results of surgery were evaluated by (a) subjective and clinical criteria and (b) associated objective changes.

Subjective and clinical improvement depended mainly on increased ability to work and relief of symptoms and signs. Favorable objective changes consisted of:

1. X-ray and Fluoroscopy: A decrease of at least 1 grade in heart size or size of the atrium. (Graded 1 to 3+ indicating slight, moderate or marked enlargement).

2. Electrocardiogram: A change toward normal of "mitral P waves," right ventricular hypertrophy or incomplete right bundle branch block pattern.

3. Hemodynamic Data: (obtained by usual technique of cardiac catheterization).[9, 10]

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a. A fall in total pulmonary resistance (30 per cent or more for preoperative values of 10 units or more).

b. An increase in the responsiveness of cardiac output to exercise (50 per cent rise above resting value on exercise in subjects with fixed output prior to surgery,) or

c. Fall in pressures in pulmonary circulation at rest and exercise if flow data were not available.

Results and Discussion

In 47 out of 81 patients (58 per cent) Aschoff lesions were found. This incidence was somewhat higher than in several other series.[2-6, 8] It was interesting to note that a normal erythrocyte sedimentation rate was found in at least 10 patients with positive biopsy; five of these were graded 3+ to 4+. No apparent relationship was found between positive auricular biopsy and the presence of atrial fibrillation.

Forty-four patients were studied carefully before and after surgery

TABLE I

RESULTS OF SURGERY IN PATIENTS WITH POSITIVE AURICULAR BIOPSY AND PREDOMINANT MITRAL STENOSIS

No. Pts.	Sex	Age	Pre-Op. Classifi. (NYHA)	Auricular Biopsy-Grade	Post-Op. Follow-up (months)	Subjective Improvement	Objective* Changes
1	F	39	III	++++	13	moderate	no
2	F	30	IV	+++	33	none	no
3	F	40	III	+++	8	moderate	yes
4	M	22	III	+	63	marked	yes
5	F	16	II	++	11	marked	yes
6	F	30	III	++	38	moderate	no
7	F	31	II	+	23	marked	yes
8	F	31	III	++	12	marked	yes
9	F	24	II	++	2	marked	yes
10	M	33	IV	+	39	dead	no
11	M	34	IV	+	32	unchanged	no
12	F	30	III	+	21	marked	yes
13	M	36	IV	++	6	marked	yes
14	M	32	III	++	5	moderate	yes
15	M	35	III	++	4	moderate	no
16	F	29	III	++	5	moderate	no
17	F	33	III	++	5	marked	no
18	F	28	IV	+	12	moderate	no

NYHA — New York Heart Association.
* — Includes favorable x-ray, ECG and hemodynamic changes.

TABLE II

X-RAY AND ELECTROCARDIOGRAPHIC (ECG) FINDINGS IN PATIENTS WITH PREDOMINANT MITRAL STENOSIS AND POSITIVE AURICULAR BIOPSY

	X-RAY			ECG				
No. Pts.	P. Op. Study (Months)	Size	LA	P. Op. Study (Months)	Rhythm	Mitral P Wave	Incomplete R.B.B.B.	RVH
1		1+	2+		NS	yes	no	yes
	3	1+	2+	7	NS	yes	no	yes
2		N	2+		NS	no	no	no
	18	1+	3+	33	AF		no	no
3		N	2+		NS	no	no	no
	8	N	1+					
4		2+	2+		NS	yes	no	yes
	41	1+	2+	34	NS	no	no	no
5		N	2+		NS	yes	no	yes
	11	N	1+	11	NS	no	yes	no
6		1+	2+		NS	no	no	no
	38	1+	2+	38	NS	no	no	no
7		N	2+		NS	no	no	no
	22	N	2+	23	NS	no	no	no
8		1+	2+		NS	yes	yes	no
				12	NS	no	no	no
9		N	2+		NS	yes	no	no
	2	N	1+					
10		N	2+		AF		no	yes
	17	1+	2+					
11		1+	2+		AF	no	yes	no
	32	1+	2+	32	AF	no	yes	no
12		2+	2+		NS	yes	yes	no
	19	2+	2+	21	NS	no	yes	no
13		3+	3+		AF		yes	no
	6	3+	2+	6	AF		yes	no
14		N	3+		AF		no	no
				5	NS	no	no	no
15		1+	2+		NS	yes	no	no
	2	1+	2+					
16		1+	1+		NS	no	no	no
	1	1+	1+	1	NS	no	no	no
17		N	2+		NS	yes	no	no
	5	N	2+	5	NS	yes	no	no
18		3+	3+		AF		yes	no
	6	3+	3+	6	AF		yes	no

LA — Left atrium.
Incomplete R.B.B.B. — Incomplete right bundle branch block.
RVH — Right ventricular hypertrophy.
P. Op. — Postoperative.

and have now been observed for an average of 12 months with the longest observations extending to 63 months. These are reported in detail elsewhere.[11] Six had predominant mitral insufficiency and were excluded from consideration of surgical results. The remaining 38 had predominant mitral stenosis, 18 of whom had positive auricular biopsy. The results of their evaluation are summarized in Tables I, II, and III. At least nine (50 per cent) of these 18 patients showed some objective changes in addition to subjective and clinical relief. The results of surgery in the group with predominant mitral stenosis and negative auricular biopsy were not significantly different (seven out of 20 or 35 per cent showed objective changes). Two of the positive biopsy group have gone through an uneventful pregnancy since surgery.

Of the entire group of 44 patients, 4 (two with positive auricular biopsy and two with negative biopsy) have had postoperative illness best classified as post-commissurotomy syndrome.[12] The first 3 have improved since surgery and the fourth, with predominant mitral insufficiency, is unchanged.

It is possible that differences in the results following surgery between the "positive" and "negative" groups may become apparent as time goes on. At present no difference has been noted and needed surgery should

TABLE III

HEMODYNAMIC DATA IN PATIENTS WITH PREDOMINANT MITRAL STENOSIS AND POSITIVE AURICULAR BIOPSY (ONLY OF CASES WITH P-OP. STUDY)

No. Pts.	P. Op. Study (Months)	PA "wedge" mm Hg. R	PA "wedge" mm Hg. X	PA mm Hg. R	PA mm Hg. X	CI L/M R	CI L/M X	SI cc. R	SI cc. X	TRP
4 G. K.				46	69	2.0	3.4	31	34	23.0
	2			24		2.3	4.0	31	40	10.4
5 J. B.		25	36	36	54	2.4	3.4	30	28	15.0
	11	15	30	24	43	2.7	5.1	32	39	8.9
7 R. M.		13		20	26	2.7	2.9	50	46	7.4
	17	9		14	20	3.0	3.5	47	46	4.6
13 R. N.		36		74	92	2.0	1.9	26	21	37.0
	6	25		50		2.3		38		21.7
14 ... D.		27	36	36	46	3.2	3.3			11.2
	4	16	20	25	39	2.6	3.9			9.6

PA "wedge" — Pulmonary artery "wedge pressure."
PA — Pulmonary artery pressure.
CI L/M — Cardiac Index in litres per minute.
SI — Stroke index in cc.
TPR — Total pulmonary resistance in $\frac{\text{PA mm Hg}}{\text{CI L/M}}$
R — Patient at rest.
X — Patient on exercise.

not be denied if "positive" biopsy is suspected. It is of interest that no "re-stenosis" has occurred in this group.

SUMMARY AND CONCLUSION

Aschoff lesions were found in 58 per cent of auricular biopsies obtained at surgery from 81 patients. Out of 44 patients studied carefully, 38 had predominant mitral stenosis; of these 38, 18 had a positive auricular biopsy. Following surgery 50 per cent of these 18 showed objective changes in addition to subjective and clinical improvement. It is suggested that the presence of Aschoff lesions in auricular biopsy does not significantly alter the surgical outcome.

RESUMEN

En el 58 por ciento de las biopsias auriculares obtenida por cirugía de 81 enfermos, se encontraron lesiones de Aschoff. De 44 enfermos estudiados cuidadosamente, 38 tenían estenosis mitral predominante, de estos 38, 18 tuvieron una biopsia auricular positiva. Después de la cirugía, 50 por ciento de estos 18 mostraroncambios objetivos además de los subjetivos y mejor a clínica. Se sugiere que la presencia de las lesiones de Aschoff en la biopsia auricular no altera significantemente la evolución postoperatoria.

RESUME

Les auteurs trouvèrent des nodules d'Aschoff dans 58% des biopsies de l'oreillette pratiquées sur 81 malades opérés. Sur 44 malades étudiés avec soin, 38 avaient une sténose mitrale prédominante; parmi ces 38 malades, 18 avaient une biopsie de l'oreillette positive. Après l'intervention, 50% de ces 18 malades présentèrent des modifications objectives ajoutées à l'amélioration subjective et clinique. Les auteurs estiment que la présence de nodules d'Aschoff dans la biopsie de l'oreillette ne modifie pas d'une façon notable l'issue chirurgicale.

ZUSAMMENFASSUNG

Aschoff'sche Knötchen wurden in 58% von aurikulären Biopsien nachgewiesen, die operativ an 81 Kranken gewonnen worden waren. Von 44 sorgfältig untersuchten Patienten hatten 38 eine überwiegende Mitralstenose; von diesen 38 hatten 18 eine positive, aurikuläre Biopsie. Nach der Operation wiesen 50% dieser 18 Fälle objektive Veränder ungen auf zusätzlich zu einer subjektiven und klinischen Besserung. Es wird die Vermutung ausgesprochen, dass das Vorliegen von Aschoff'schen Knötchen bei aurikulärer Biopsie die operativen Ergebnisse nicht wesentlich beeinflusst.

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Chronic Disseminated Tuberculosis*

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Tuberculosis is a generalized disease most commonly localized in the pulmonary system. The rapid dissemination is well known as miliary tuberculosis and acute generalization, but the chronic metastasizing form is less frequently recognized. Chronic disseminated tuberculosis is defined by us when the disease is prolonged and involves several organs of the body. This type of tuberculosis will be discussed with the results obtained from antituberculous therapy.

An extensive literature has arisen in the treatment of clinical tuberculosis by the different specialty groups such as Orthopedics for bone tuberculosis, Urology for renal tuberculosis and Gynecology for genital tuberculosis, etc., managing each as a localized disease. Nevertheless, this condition is a generalized one as can be demonstrated in the following cases.

Case 1: This 23 year old Negro soldier was well until the winter of 1950 when he gradually developed fever, anorexia and weight loss. He was admitted to the U. S. Army Hospital in Germany during February, 1951 where he received penicillin for 20 days with no clinical response, followed by two weeks of streptomycin and aureomycin. He was discharged from the hospital with a history of 25 pounds weight loss, weakness, and anorexia. During the summer of 1951 he continued to lose weight, had drenching night sweats and developed pain and stiffness in the region of his right hip which gradually grew worse. He was again hospitalized in February, 1952 for fever, weight loss, anorexia, night sweats, bloody diarrhea, and a cystic mass noted anteriorly to the sternum.

Physical examination revealed a chronically ill, emaciated Negro weighing 116 pounds with temperature of 101° F. and a pulse of 120 per minute. A six centimeter mass was found on the anterior surface of the sternum extending from the third to the fifth rib.

Laboratory data and chest roentgenogram were within normal limits. Anteroposterior and lateral thoracic and lumbar roentgenograms revealed a bilateral paravertebral mass extending from the fifth to the tenth thoracic vertebrae with slight narrowing of the intervertebral space between the eighth and ninth vertebrae, but no evidence of bony destruction. First strength PPD was positive (2+). Serological test for syphilis, repeated blood cultures, an upper gastrointestinal series, cholecystogram, intravenous pyelogram and cystoscopy were negative or within normal limits. Red blood cell count was 2,540,000, with hemoglobin of 7 grams; white blood cell count was 7,750 with normal differential. Total serum protein 7.54 grams per 100 cc. of which albumin was 3.75 grams. Acid fast bacilli were isolated from the cystic mass on the chest and M. tuberculosis was later cultured.

Course: He was treated with 2 grams of streptomycin every third day and PAS, 12 grams daily from July 19, 1952 to August, 1952 when streptomycin was reduced to 1 gram twice weekly with PAS, 12 grams daily until May, 1954. His temperature ranged from 101° F. to 104° F. until August 5, 1952 when it became normal. The cystic mass and paravertebral masses had disappeared by November, 1952 with the patient weighing 125 pounds. On November 25, 1952 a Hibbs spinal fusion of the third to the 12th thoracic vertebrae was performed under sodium penthothal and nitrous oxide anesthesia. On December 29, 1952 a second fusion operation was done on the lumbosacral joint using iliac bone chips. His postoperative courses were uneventful, and when he was discharged to duty in May, 1954 he was free of symptoms, except for backache, and weighed 160 pounds.

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Case 2: This 24 year old Negro veteran suddenly developed blurring and decreased vision in the right eye in August, 1952 at Ladd Air Force Base, Alaska. This rapidly progressed until only a light perception remained. He was found to have an exudative lesion in the right eye with detached retina for which surgery was performed but with poor result. He was discharged from the Air Force in February, 1952.

While working as a truck driver he states that he struck his left elbow against the tail board of a truck. He had pain momentarily but no swelling or stiffness. Approximately two weeks later he noticed increasing stiffness, discomfort and swelling in the left elbow. A roentgenogram showed a destructive and proliferative lesion in the proximal third of the ulna. His symptoms grew progressively worse and a biopsy was obtained on August 4, 1953 demonstrating acid fast bacilli in the exudate and on pathological sections. A transfer was later made to Letterman Army Hospital.

Physical Examination: Height 73 inches, weight 160 pounds, temperature 98.6° F., pulse 92, blood pressure 110/70 mm. of Hg. The right eye showed an organized cicatricial granulomatous mass of the ciliary body and iris at 9 o'clock. Marked swelling with redness, increased heat and tenderness with a 2 inch incision on the dorsal surface of the right elbow was present.

Laboratory Data: Chest roentgenogram in February, 1953 and on admission showed an indiscreet hazy nodular density in the right apex with no evidence of calcification and a rounded area of increased density in the right fourth interspace posteriorly. Left elbow roentgenogram revealed a destructive process at the proximal end of the ulna with a periosteal reaction and distention of the joint capsule. The joint surfaces of the ulna and the humeral epicondyle were roughened. Serological test for syphilis was negative. White blood cell count was 8,650 with 67 per cent neutrophils, 22 per cent lymphocytes, 10 per cent monocytes and 1 per cent eosinophils. Hemoglobin was 12.3 gms. Urinalysis was negative. Sedimentation rate was 25 mm/hour.

Course in the Hospital: Streptomycin, 1 gram twice weekly and PAS, 12 grams daily were begun on August 17. While in the hospital he maintained a temperature of 100° F. which returned to normal after three weeks. The left elbow showed complete disappearance of swelling, heat and tenderness with only slight limitation in motion. Late in September he was transferred to the Veteran's Administration Hospital.

Case 3: A 19 year old Negro soldier was first seen at Camp Roberts, California, on September 9, 1953 for nasal congestion, headache and backache. Chest roentgenograms showed bilateral mediastinal adenopathy with an area of infiltration in the left lower lung field. He was transferred to Letterman Army Hospital where physical examination revealed an essentially healthy appearing man.

Laboratory Data: On admission urine and serology test for syphilis were normal or negative. First strength PPD was positive and coccidioidin skin test was negative. Routine laboratory tests were within normal limits. The sedimentation rate was 38 mm./hour (Wintrobe). Total proteins were 8.8 grams per 100 cc., of which albumin was 3.8 grams and globulin 5.3 grams. Gastric washings were positive for M. tuberculosis on culture.

Course: A liver biopsy was performed showing on some portions of the sections granulomatous nodules. He was treated for active tuberculosis with streptomycin, 1 gram twice weekly and PAS, 12 grams daily and later transferred to Fitzsimmons Army Hospital.

Case 4: A 22 year old Negro was admitted to Oliver General Hospital, Augusta, Georgia in August, 1947 with a history of a continuous low grade fever and a 30 pound weight loss over approximately 20 months. Shortly after admission he developed a mass (2 cm. in diameter) in the medial aspect of the middle third of the left arm which was excised in early September, revealing typical caseating tuberculosis with acid fast organisms seen and later demonstrated on culture. The patient was then placed on 1 gram of streptomycin daily. One month later he complained of back pain. X-ray film showed a destructive lesion in the bodies of the 10th and 11th thoracic vertebrae. He was then treated for bone tuberculosis by a Bradford frame. The skin lesion promptly healed. After eight months the bone lesions showed considerable healing. He was continued on streptomycin and orthopedic treatment for one year with apparent healing of the bone lesions.

Case 5: This 19 year old Negro was admitted to the Letterman Army Hospital on March 13, 1954 with fever of undetermined origin. He had a three month history of frequent upper respiratory infections and symptoms of malaise, mild chest pain and productive cough. Just prior to admission, he had received four days of treatment with penicillin and five days of treatment with terramycin, with some symptomatic improvement but no change in daily temperature elevation to 102° F. There had been a 25 pound weight loss in the 11 months prior to admission. Physical examination

revealed fine expiratory rales at the right apex, posteriorly. There was a single, large, rather movable nontender node in the supraclavicular area, the axilla and the epitrochlear area on the right side.

Smear, culture and guinea pig inoculation of the sputum and gastric washings were negative for acid fast bacilli. The right supraclavicular lymph node was removed and was positive for acid fast bacilli on direct smear, and on guinea pig inoculation for M. tuberculosis. X-ray film of the chest revealed apical infiltration, right hilar and paratracheal adenopathy. He ran a Pel-Ebstein type of fever curve, with temperature elevations to 103° F. until March 29. He was placed on isoniazid and streptomycin on March 27, with marked improvement of symptoms.

Case 6: This 15 year old underdeveloped and undernourished colored girl had fusion of the thoracolumbar vertebrae for tuberculosis in 1943. In 1948 she was hospitalized in Gorgas Hospital because of a tuberculous abscess of the right thigh. This healed under streptomycin therapy and her chest x-ray films was negative. She was hospitalized again in 1952 because of tuberculous cervical adenitis with sinus formations. This healed under streptomycin, isoniazid, streptokinase and streptodornase therapy. She was discharged from the hospital after six months of treatment. She was readmitted in November, 1954 with tuberculous lymphadenitis in the right inguinal area. Purulent material from this area contained acid fast bacilli. She was treated with streptomycin and isoniazid for a period of four months. The sinus closed and she was discharged in January, 1955 to continue on treatment indefinitely as an outpatient. At present, there is no evidence of newly developed tuberculous lesions.

Case 7: This 29 year old colored woman was under observation of the chest clinic, Gorgas Hospital from September, 1952, for an infiltration in the upper lobe of the left lung which was compatible with tuberculosis. The lesion at that time was thought to be stable. In January, 1953 she was admitted to the Gynecology Service for dilatation, curettage and conization of the cervix for so-called carcinoma in situ. The pathologist reported tuberculous endometritis and acute and chronic cervicitis.

Routine laboratory examinations were negative, sputum and gastric washes (15) were all negative and acid fast bacilli including cultures. She was treated with streptomycin and isoniazid. Repeated dilatation and conization revealed normal endometrium. Serial x-ray films of the chest showed marked regression of the infiltrative process in the left upper lobe. After nine months on streptomycin and isoniazid, she had total hysterectomy. Serial sections of the cervix and uterus failed to show evidence of carcinoma or tuberculosis. In January, 1956, she began to have backache and tenderness over the third and fourth lumbar vertebrae. X-ray films of the spine showed suspicious areas of rarefaction compatible with tuberculosis. She is on the orthopedic service again receiving antituberculous medication.

Case 8: This 17 year old Panamanian girl was admitted to Gorgas Hospital in 1944 because of fever, diarrhea and vomiting. The diagnosis at that time was gastroenteritis and suspicious pulmonary tuberculosis involving the left apex. She returned in 1950 when her sputum contained acid fast bacilli. The chest x-ray film showed diffuse nodular densities throughout both lung fields. She was hospitalized and placed on streptomycin and PAS. Four months later pneumoperitoneum was started. She improved and was discharged from the hospital in August, 1955 as an arrested case of pulmonary tuberculosis and with the recommendation to continue pneumoperitoneum. This was done, and she had chest x-ray films every six weeks. However, in May, 1952 she was admitted to the hospital because of an infection in her right ankle. X-ray films revealed evidence of infectious arthritis with diffuse osteoporosis of the bones of the foot. On May 23, 1952 biopsy revealed chronic granulomatous reaction of the ankle joint compatible with tuberculosis. She was placed on streptomycin and isoniazid. The ankle was placed in a short leg cast and she remained on this treatment for nine months. At present, she is asymptomatic and has had fusion of the right ankle. The lesion in the lung apparently is inactive.

Case 9: This two year old Panamanian girl was admitted to Gorgas Hospital in December, 1947 because of osteomyelitis of the left tibia. Chest x-ray film at that time showed evidence of disease in the left lung with suspicious atelectasis. A repeat chest x-ray film two months later revealed evidence of infiltration in both lung fields and enlarged hilar and paratracheal nodes. She reacted to the first dose of PPD. Over the left malleolus an ulceration was found with a draining sinus. Material from this area contained acid fast bacilli. A cast was employed for six months, when an x-ray film showed improvement of the disease of the metaphysis and diaphysis of the left tibia and regression of the pulmonary infiltration. She was discharged in May, 1948 and followed as an outpatient. The cast was removed in the latter part of 1948 and until February, 1955 she had no more trouble. In February, 1955 she began to

run a low grade fever and to have pain in the right hip. The fever did not respond to any of the wide spectrum antibiotics. X-ray film of the pelvis, femur and chest revealed no abnormality. She reacted to the first dose of PPD. Due to the past history it was decided to administer isoniazid, 4 mg./kilo per day. She became afebrile after six days and the hip pain subsided on the 10th day. She is still receiving isoniazid and will continue on this drug for a period of eight to twelve months.

Case 10: This 47 year old colored man was followed in the chest clinic, Gorgas Hospital because of an infiltration in the upper lobe of the left lung from November, 1951. He had been hospitalized on multiple occasions for evaluation of this lesion. Sputa, gastric and bronchial washes were negative for acid fast bacilli, including cultures and guinea pig inoculation.

Around January, 1952 he began to complain of sore throat for which he was referred to nose and throat service. He was seen there on many occasions and the diagnosis was hypertrophy of the lingular tonsils. On one occasion he received x-ray treatment to this area. In July, 1952 he returned to the chest clinic where an x-ray film showed no change in the infiltration. However, the throat pain persisted. Indirect laryngoscopy revealed ulceration at the base of the tongue. Biopsy proved it was tuberculous. After three months on streptomycin and isoniazid, the ulcer healed completely and the infiltration in the lung regressed. In September, 1952 bronchoscopy revealed no endobronchial disease. He remained on drugs from July 7, 1952 to February 6, 1953. At present he is asymptomatic, with no apparent change in the lesions.

Case 11: This 32 year old colored woman complained of a nontender "lump" in the left breast two weeks prior to admission to Gorgas Hospital. She had received penicillin and terramycin with no effect on this mass. During this period she noticed a painful mass under the angle of the left mandible and had low grade fever. Physical examination was essentially negative with the exception of two nontender small nodules inferior to the left ear lobe and two large somewhat fixed, nontender nodes in the left axilla. A freely movable nontender three centimeter diameter mass was found in the left breast. Routine laboratory tests were within normal limits. An x-ray film of her chest was negative. The erythrocyte sedimentation rate was 37 mm. in one hour. She reacted to the first dose of PPD.

On May 10, 1955 biopsy of a node near the angle of the left mandibular revealed tuberculosis. On May 13, she was started on streptomycin and isoniazid, after which the lesions decreased in size. However, biopsy of the mass in the left breast on June 27, revealed disease "compatible with tuberculosis." She was discharged asymptomatic on August 16, 1955 to continue on streptomycin and isoniazid as an outpatient.

Discussion

All patients in the present series were chronically ill with persistent fever and weight loss. The first, fourth and fifth cases had fever with weight loss of approximately 40 pounds over a period of twenty months. They underwent multiple investigative procedures but tuberculosis was not suspected until masses appeared which were biopsied. Under antituberculous therapy, symptoms promptly subsided, and the patients regained their weight. It is our opinion that a clinical trial with antituberculosis drugs is warranted in the presence of undiagnosed prolonged fever, weight loss and positive tuberculin reaction.

In the second case, tuberculosis was not considered by the ophthalmologist as the etiological factor of the eye and lung pathology until tuberculous osteomyelitis was found. Again it is pointed out that in exudative or granulomatous lesions in the eye with a positive tuberculin, antituberculous therapy should be instituted.

In the presence of roentgenographic findings and no other clinical manifestations of tuberculosis, liver biopsies can also show the presence of granulomatous lesions. This was demonstrated in the third case in which there was mediastinal adenopathy, parenchymal lung disease, and a granulomatous lesion compatible with tuberculosis in the liver.

The sixth case had spinal fusion for tuberculosis of vertebrae in 1943. Five years later, 1948, she had tuberculous osteomyelitis of the right femur with a draining sinus, receiving streptomycin with apparent healing. Cervical adenitis and multiple draining sinuses occurred in 1952. Combined isoniazid and streptomycin for six months resulted in marked improvement. In 1954, tuberculous adenitis of the right inguinal area was treated with isoniazid and streptomycin. This patient reveals the chronicity and the multiplicity of sites in which chronic disseminated tuberculosis occurs and the difficulty in completely eradicating foci. This case demonstrates that therapy should be prolonged.

A stable lung lesion was present in the seventh case with negative gastric cultures. Seven months later, dilatation and curettage revealed tuberculous endometritis with positive culture. The patient received six months of combined streptomycin and isoniazid therapy followed by hysterectomy. Serial sections of the uterus revealed no evidence of tuberculosis in the endometrium or cervix. However, two years later, with a stable lung lesion, she was admitted to the hospital with destructive lesions in the fourth and fifth lumbar vertebrae compatible with tuberculosis. This case demonstrates that antituberculosis drugs were sufficient to eradicate the disease in the uterus but not to eliminate all foci.

Cases eight and nine show pulmonary and bone tuberculosis. The bone lesions manifested themselves much later although treatment of the lung had been instituted. Case eight received streptomycin and PAS for a period of six months along with pneumoperitoneum. The lung lesion was stabilized and the pneumoperitoneum was continued for a period of two years, when tuberculosis of the malleolus became evident and healed under antituberculosis drugs with fusion of the ankle. Case nine, a child with tuberculosis of the malleolus healed on conservative orthopedic treatment. Seven years later, she developed low grade fever of about three months duration which did not respond to the various wide spectrum antibiotics; the fever subsided, however, within 10 days after isoniazid therapy was instituted. These cases again point out the chronicity and recrudescence of tuberculosis even after receiving short term chemo-antibiotic therapy.

Two infrequent locations for tuberculosis were observed in the last two cases. Case 10 had pulmonary tuberculosis with a tuberculous ulcer of the tongue and Case 11, tuberculous cervical adenitis with tuberculous mastitis. The lesions healed adequately under specific medication.

Tuberculosis is not an isolated organ disease with pulmonary, kidney or skeletal involvement but is more generalized even when one can only demonstrate involvement of one organ. One of us (E.C.) performed liver biopsies in active pulmonary tuberculosis finding granulomatous lesions in the liver of 30 per cent of such biopsies.

Since the advent of the chemo-antibiotic agents, a definite diagnosis in chronic tuberculosis can no longer be considered of purely academic interest; it is imperative to make the diagnosis early and to treat it vigorously. Tuberculosis must be treated then as a generalized disease and not as a localized process. In view of the accumulated evidence that prolonged

isoniazid in conjunction with streptomycin and/or Para-aminosalicylic acid is the therapy of choice in pulmonary tuberculosis, such a regimen would likewise seem to be indicated in chronic disseminated tuberculosis. The authors feel that with early diagnosis and adequate therapy with the available antituberculosis drugs, the prognosis will improve. In these cases, one must explore the possibility of prolonged, perhaps life long treatment with chemo-antibiotic agents, especially isoniazid. The residuals in the specific organs after prolonged drug administration can be treated by the accepted procedures recommended by different specialists. This combined form of therapy should markedly improve the results.

SUMMARY

Chronic disseminated tuberculosis is a prolonged disease which involves several organs of the body. It is not easily recognized. Any person with prolonged undiagnosed fever, weight loss and positive tuberculin deserves a trial with antituberculosis drugs. Eleven cases are presented to illustrate the multiple organ involvement in chronic disseminated tuberculosis and the results obtained with antituberculosis drugs. Treatment of this disease must be generalized and prolonged. Residuals in involved organs after prolonged drug administration should be treated by procedures recommended by appropriate experts.

RESUMEN

La tuberculosis crónica diseminada es una enfermedad prolongada que compromete varios órganos del cuerpo. No es fácilmente reconocida. Cualquiera persona con fiebre prolongada no identificada, pérdida de peso, y reacción tuberculínica positiva, requiere untratamiento con drogas antituberculosas.

Se presentan once casos para ilustrar el compromiso de múltiples órganos en la tuberculosis crónica diseminada y los resultados obtenidos después de las drogas antituberculosas.

El tratamiento de esta enfermedad debe ser generalizado y prolongado. Los residuos en los órganos atacados, después de prolongado tratamiento deben ser tratados por métodos de acuerdo con los expertos.

RESUME

La tuberculose chronique disséminée est une maladie de longue durée qui atteint plusieurs organes. Elle n'est pas facilement reconnue. Toute personne qui est atteinte d'une fièvre à long cours indéterminée, qui subit une perte de poids, et a une réaction tuberculinique positive, est justiciable d'un essai de traitement par les médications antituberculeuses. Les auteurs présentent onze cas pour illustrer l'atteinte multiple des organes dans la tuberculose chronique disséminee, et les résultats obtenus avec les médications antituberculeuses. Le traitement de cette affection doit être généralisé et prolongé. Les atteintes viscérales séquellaires après administration prolongée des médications devraient être traitées par les moyens recommandés par les spécialistes.

ZUSAMMENFASSUNG

Die chronische disseminierte Tuberkulose ist eine anhaltende Krankheit, in die mehrere Organe des Körpers eimbezogen sind. Sie ist nicht leicht zu erkennen. Jeder Fall mit anhaltendem unerkanntem Fieber, Gewichtsabnahme und positiver Tuberkulin-Reaktion ist einen Behandlungversuch mit antituberkulösen Mitteln wert. Es werden 11 Fälle beschrieben, um die multiple Organbeteiligung bei chronischer disseminierter Tuberkulose zu veranschaulichen sowie die mit antituberkulösen Mitteln erzielten Ergebnisse. Die Behandlung dieser Krankheits muss eine generalisierte und anhaltende sein. Restzustände an befallenen Organen nach anhalftender medikamentöser Behandlung müssen so behandelt werden, wie es die auf diesem Gebiet erfahrenen Experten raten.

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A New Method for Antibiotic Sensitivity Testing of Bronchial Flora

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Routine methods for testing drug sensitivity of microflora in secretions aspirated at bronchoscopy appear to be impractical because reports cannot be obtained for 36 to 48 hours. Patients are often hospitalized for short periods and relatively little time is available for aerosol therapy or other treatment with effective drugs. Furthermore, present techniques for determining drug sensitivity of bronchial microflora often favor an overgrowth of extrinsic microorganisms not responsible for the pathological condition, while the more delicate pathogens are excluded. Inaccuracies in determining drug sensitivity often result from these procedures, and a poor correlation between laboratory reports of drug activity and *in vivo* effectiveness is observed.

The method[1, 2] reported in this paper reduces the time required for sensitivity testing to 12 to 24 hours and permits better growth of the microflora responsible for the pathology observed. Consequently, it is possible to initiate drug therapy soon after the patient is bronchoscoped and thus maintain treatment for a longer period of time with drugs specific for the infection. The method is economically feasible for the patient and may be employed at no greater expense than routine laboratory procedures.

Materials and Methods

All tests were made using tryptose blood agar base (Difco Laboratories) containing blood from outdated blood bank specimens. The sensitivity tests, conducted with "Multidiscs" distributed by Case Laboratories, used two or three concentrations of each drug.

The method described below is hereafter referred to as the "Direct Dilution Method." Approximately 5 cc.'s of each bronchial secretion specimen obtained at bronchoscopy was diluted with 5 to 15 cc.'s of 5 per cent sterile dextrose solution and emulsified. Up to 10 cc.'s of each specimen was incorporated in 125 cc.'s of melted blood agar base previously cooled to 45° C. Blood was added to a concentration of 3 to 4 per cent. After thorough mixing, six plates, each containing 20 cc.'s of the inoculated medium, were poured and allowed to solidify. The appropriate test discs were then placed on the surface of the medium and the cultures incubated at 37° C. For comparison, duplicate determinations were conducted ac-

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cording to a routine method in which tubes of brain-heart infusion broth were inoculated with a portion of the specimens. After 12 to 24 hours incubation, the resulting bacterial growth was streaked on the surface of tryptose blood agar plates. A total of 19 drugs, including penicillin, 10 broadspectrum antibiotics, six sulfonamides and two nitrofurantoin compounds, were used in all tests. The zones of inhibition around the discs were measured in millimeters at 4, 12 and 24 hours.

Results

A comparison of the effectiveness of the Direct Dilution Method with routine procedures was made using penicillin as the representative antibiotic (Table I). It may be observed that by the Direct Dilution Method, over 89.6 per cent of the 69 specimens exhibited flora sensitive to penicillin and approximately 10.4 per cent contained resistant microorganisms. Conversely, by routine methods, only 44 per cent of the specimens tested exhibited penicillin sensitive bacteria while resistant cultures occurred in 56 per cent of the samples.

In the instances in which penicillin was indicated to be effective, according to the Direct Dilution Method, good patient response was obtained in an estimated 90 to 95 per cent of the cases treated with penicillin aerosol therapy. In marked contrast, routine sensitivity methods indicated penicillin to be effective in much smaller percentages, but when it was used in these circumstances, equally good patient response was observed. Careful clinical observations, carried out over a three-year period, have corroborated these impressions of the more limited group reported here.

Discussion

The Direct Dilution Method appears to have several advantages over routine sensitivity testing techniques. Using this method, the microflora of the bronchial secretions are immobilized in the solid medium. This condition permits their growth in proportion to the frequency of their occurrence in the specimen; consequently, the more fastidious pathogens have an opportunity to develop without being overgrown by more rapidly metabolizing organisms of a saprophytic or nonpathogenic status. By the routine method, on the other hand, the rapidly metabolizing organisms

TABLE I

A COMPARISON OF METHODS FOR DETERMINING THE EFFECTS OF PENICILLIN ON THE BACTERIAL FLORA OF BRONCHIAL SECRETIONS AND SPUTUM SPECIMENS

	Sensitive (More Than 4 mm.) Per Cent	Slightly Sensitive (4 mm.) Per Cent	Resistant (Less Than 4 mm.) Per Cent
Direct Dilution Method 69 Specimens	84.5	5.1	10.4
Routine Culture Method 74 Specimens	39.9	4.1	56

may overgrow the culturally delicate pathogenic bacteria in the brain-heart medium. As a result, sensitivity tests conducted by this method may indicate drug response of organisms not actually involved in the pathological condition rather than drug sensitivities of the flora responsible for the infection. Thus, the more economical drugs, such as penicillin, often are not recommended for conditions where these drugs frequently would be effective.

Reduction of the time required for sensitivity testing by the Direct Dilution Method is of importance in permitting early initiation of appropriate drug therapy. Accurate results can be obtained in 4 to 24 hours, since the evaluation may be made on the basis of changes in the blood medium due to the metabolic activity of the microflora, i.e., hemolysis, opacity, etc., and may be observed prior to the appearance of detectable macroscopic bacterial colonies. Reports such as those of Rammelkamp and Maxon,[3] Schmidt and Lester,[4] Gezon,[5] and others[6] have inferred that penicillin is becoming an unsatisfactory therapeutic agent in the treatment of respiratory infections. The authors agree that it has lost some of its original effectiveness due to the development of penicillin resistant bacteria; however, the relatively close correlation between results obtained with the Direct Dilution Method of sensitivity testing and the clinical response indicates that penicillin is still a highly effective agent in the treatment of many such infections. Since this method is no more complex than routine techniques and requires only the usual laboratory materials and media, it may be employed as economically as other methods currently in use. The method is also applicable in testing sputum specimens, although it must be recognized that the unavoidable contamination of the specimen by mouth organisms may render the results less accurate.

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SUMMARY

1. A new Direct Dilution Method, which is more rapid and permits a more accurate evaluation of drug effectiveness, is described for the sensitivity testing of bronchial flora. The steps of the procedure are as follows: (a) Homogenize one part of bronchial secretions with three parts 5 per cent dextrose water. Amounts may be varied depending on the viscosity of the secretions. (b) Incorporate up to 10 cc.'s of homogenate into 125 cc.'s of tryptose blood agar base containing 5 cc.'s of defibrinated blood at a temperature of 45° C. (c) Mix well and distribute into petri dishes (six for above amount). Allow to solidify and apply test discs ("Multidiscs"—Case Laboratories). (d) Incubate at 37° C. and read at 4, 12 and 24 hours. (e) Measure from the periphery of the test disc to the initial growth zone and report in mm. The reading is based on the visible indications of bacterial metabolism in the media (i.e., hemolysis, turbidity, etc.).

2. The method overcomes certain disadvantages encountered in routine methods of testing and has been found to be as economical for the patient

as methods currently employed.

3. The data presented would indicate that penicillin is still a highly effective antibiotic in the treatment of respiratory infections.

4. Careful clinical observations have tended to corroborate the accuracy of the laboratory results.

RESUMEN

1. Se describe un nuevo método de dilución directa que es más rápido y permite una mayor exacta evalución de la efectividad de las drogas frente a la flora bronquial. El procedimiento es como sigue: (a) Se homogeniza una parte de secreciones bronquiales con tres partes de una solución de dextrosa al 5 por ciento.

Las cantidades pueden ser variadas dependiendo de la viscosidad de las secreciones. (b) Se incorporan 10 cc. de este producto homogenizado a 125 cc. de triptosa-agar-sangre, conteniendo 5 cc. de sangre desfibrinada a la temperature de 45°C. (c) Mezclar bien y distnribuir en seis cajas de Petri (en cantidad de 60 mas). Déjese solidificar y colóquense los discos de prueba ("Multidiscs" Laboratorio Case). (d) Incúbese a 37°C. y léanse a las 4, 12 y 24 horas. (e) Mídase a partir de la periferia del disco de prueba hacia la zona de inicial de crecimiento de colonias y apúntese en milímetros. La lectura se basa en las indicaciones visibles del metabolismo bacteriano en el medio (es decir hemolisis, turbidez, etc.).

2. El método resuelve algunas desventajas que tienen los métodos usuales y se ha encontrado que es económico para el enfermo, tanto como los metodos corrientemente empleados.

3. Los datos presentados indicarían que la penicilina es aún un antibiótico altamente eficaz en las infecciones respiratorias.

4. Las cuidadosas observaciones clínicas han tendido a corroborar la eficacia de los resultados de laboratorio.

RESUME

1. Les auteurs décrivent une nouvelle méthode directe de dilution pour tester la sensibilité de la flore bronchique. Elle se montre plus rapide et permet une estimation plus précise de l'efficacité des médications. Les différentes phases de cette technique sont les suivantes: (a) Homogénéisation d'une partie de sécrétions bronchiques avec trois parties d'eau dextrosée à 5%. Les quantités peuvent varier selon la viscosité des sécrétions. (b) Incorporation de 10 cc. de l'homogénéisation dans 125 cc. de gélose au sang tryptosé contenant 5 cc. de sang défibriné à la température de 45°C. (c) Bien mélanger et distribuer en boites de Pétri (six pour la quantité ci-dessus mentionnée). Laisser solidifier et disposer les disques-tests ("Multidiscs" Case Laboratories). (d) Laisser à l'étuve à 37°C. et lire après 4,12 et 24 heures. (e) Mesurer de la périphérie du disque-test jusqu'à la zone initiale de culture, et reporter en millimètres. La lecture est basée sur les indications visibles du métabolisme bactérien dans le milieu (c'est-à-dire hémolyse, état trouble, etc.).

2. La méthode combat certains inconvénients rencontrés dans les méthodes de routine et s'est montrée aussi économique pour le malade que les

autres méthodes couramment employées.

3. Les résultats apportés montrent que la pénicilline est encore un antibiotique hautement efficace dans le traitement des infections respiratoires.

4. Des observations cliniques soigneuses permettent de confirmer l'exactitude des résultats de laboratoire.

ZUSAMMENFASSUNG

1. Es wird eine neue direkte Verdünnungsmethode beschrieben, die schneller vonstatten geht und eine genauere Bestimmung einer Arzneiwirke samkeit ermöglicht, zum Zwecke der Sensibilitätsprüfung der Bronchial-Flora. Folgendes sind die einzelnen Stufen des Vorganges: (a) Homogenisierung von 1 Teil Bronchialsekret mit 3 Teilen 5% Dextrose-Wasser. Die Mengen können wechseln je nach der Viscosität der Sekrete. (b) Zusatz von bis zu 10 ccm der homogenisierten Flüssigkeit zu 125 Tryptose-Blutagar als Grundlage, dem 5 ccm defibrinierten Blutes zugesetzt sind bei einer Temperatur von 45°. (c) Gute Durchmischung und Verteilung in Petrischalen (6 für obige Menge), Erstarren lassen und Verwendung von Testschalen ("Viel-Schalen" Laboratoriumsmethode). (d) Im Brutschrank halten bei 37° und ablesen nach 4,12 und 24 Stunden. (e) Ablesung von der Peripherie der Testschalen zur initialen Wachstumszone und Bericht in mm. Die Ablesung geht so von sichtbaren Anzeichen bakteriellen Stoffwechsels im Medium aus (d.h. Haemolyse, Trübung usw.).

2. Mit dieser Methode werden gewisse Mängel überwunden, die bei den üblichen Testmethoden auftreten, und sie hat sich als ebenso wirtschaftlich erwiesen für den Kranken wie die laufend benutzten Verfahren.

3. Die vorgelegten Daten begen einen Hinweis darauf, das das Penicillin noch immer ein hoch wirksames Antibiotikum ist bei der Behandlung von Infektionen des Respirationstraktes.

4. Sorgfältige klinische Beobachtungen hagen dazu beigetragen, die Genauigkeit der Laboratoriums-Ergebnisse zu bestätigen.

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Industrial Diseases of the Chest: A Commentary on Current Problems*

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With increasing industrial activities all over the world, pulmonary lesions caused by inhaled dusts, fumes and gases have become steadily more numerous. Several of these pneumopathies are well known though previously rather rare entities. Larger numbers of industrial workers have lately become involved. Other diseases are new. Among the more recently identified conditions are suberosis, caused by inhaled cork dust; canabosis, occurring in hemp workers; berylliosis, due to exposures in fluorescent and radio tube and atomic energy industries. Chronic irritation of the respiratory tract mucosa has been observed in the plastic producing industries, textile industries in which bleaching is an important phase, and galvano-plasty industries exploiting chrome and nickel.

Owing to the multiplicity of causative factors and regional differences in industrial practices, the chemical manifestations of the occupational chest diseases are very variable. This has led to considerable conflict of opinion concerning their true significance. One of the problems which has most stubbornly resisted solution is the discrepancy between the radiological features and the clinical findings in the pneumoconioses. It long has been known that advanced x-ray changes indicative of silicosis are compatible with minimal disability. It recently has become apparent, however, that dyspnea and asthma may reach great intensity in silicotics before the pulmonary changes are recognizable radiologically. These bronchitic and asthmatic syndromes in silicotics should be differentiated from occupational asthma such as may be caused by inhaled organic substances which have become specific allergens in individual cases (flour, linseed oil, cotton, hemp, drugs, hair, feathers, fungi, parasites). Asthmatic reactions are also fostered by unfavorable environmental conditions such as may prevail in the vicinity of furnaces, refrigeration plants or draughty and humid work areas. The inorganic dusts produce bronchitic and asthmatic states which are associated with anatomical as well as functional changes in the lung. In some instances the respiratory distress appears to be a delayed result of the pneumoconiotic process and in other instances it may be a direct and more immediate sequel to the inhalation of hazardous

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dusts. In up to 80 per cent of silicotics with dyspnea, alterations of the peri-nasal sinuses have been encountered. It is not clear what relationship such sinusitis has to the bronchitis. Clarification is needed of the relationship between infectious, allergic, sinoid and silicotic bronchitis. Elucidation of the significance of these bronchitides in the genesis of emphysema and pulmonary or bronchial vascular disturbances appears to be a field for further experimental and clinical investigation.

During the past several decades, clinicians have observed material changes in the pattern of pneumoconiotic roentgenographic abnormalities. Part of this is due to the improvement of x-ray techniques. Macroradiography by means of fractional focus tubes has revealed parenchymatous pulmonary lesions not previously identifiable. The major change, however, is real. The pathology of the pneumoconiotic process in miners and sandblasters has been modified by the rigorous application of prophylactic engineering techniques. The introduction of wet drilling, furthermore, has resulted in the predominance of submicron particles in the working atmosphere, with sequential effect on the character of the resulting pneumoconioses. The avoidance of siliceous exposures in coal and iron mines also has placed emphasis on the role of iron or coal dust *per se* versus the combined effect of anthracotic or ferrous and quartzitic particles. The reduction in the prevalence of tuberculosis in rock workers has further modified the clinical character of the pneumoconioses. It also has become apparent recently that the delicate reticular or granular x-ray patterns commonly seen in a variety of benign pneumoconioses are the radiographic equivalents of perivascular and peribronchial deposits of non-fibrosing dusts.

It long has been recognized that pulmonary emphysema is a regular and serious concomitant of advanced silicosis. Its origin has been sought variously as a manifestation of compensatory alveolar distension around cicatricial nodular scars and indurated perivascular and peribronchial tissues. The possibility that the emphysema may arise as a result of a bronchostenotic or of a check-valve mechanism at various points along the respiratory passages also deserves consideration. Focal emphysema has also recently been identified as an autonomous dust-induced bronchiolectatic entity. The prior use of the term perifocal emphysema has caused a little confusion in the understanding of focal emphysema as defined by the Cardiff School. Recognition should also be accorded to a neurogenic variety of emphysema which may arise through ganglion cell degeneration as a result of inhalation exposures to toxic substances such as cadmium. Differential diagnosis between so-called senile emphysema or of idiopathic or constitutional emphysema on the one hand and emphysema of pneumoconiotic origin on the other remains a clinical conundrum, particularly in the elderly industrial workers. A radiologic clue may be found in the dispersed character of non-industrial emphysema, while emphysema sequential to pneumoconiosis tends to have regional dominances.

The classification of radiographs in the pneumoconioses continues to present difficulties. While the system proposed in 1930 at the First Inter-

national Conference on Silicosis at Johannesburg errs on the side of oversimplification, the most recent scheme suggested at the Third International Conference at Sydney in 1950 may be somewhat overelaborate. The Johannesburg classification was too strongly influenced by the pathology of silicosis in gold mines to be universally applicable to pneumoconioses of different etiology. It has become apparent too that not all silicotic states necessarily evolve through all three stages in the order suggested by the classification. Recent newer radiographic techniques have also defined pneumoconiotic entities which cannot be accommodated within the somewhat rigid confines of this form of systematization.

The Sydney scheme has undeniable advantages in the interpretation or description of radiographs of coal miners having its origin in the work on anthracotics at Cardiff. This classification provides for improved quantitative estimation of the pulmonary disease, furnishes qualitative descriptions and differentiates between fine versus extensive opacification. It does not, however, mention tuberculosis, its quantitative criteria remain arbitrary, and it is poorly adaptable to statistical elaboration. Nevertheless, because of its greater flexibility, this 1950 classification is gaining acceptance not only in its country of origin but also in Germany.

The relationship between pulmonary tuberculosis and silicosis requires further exploration. Tuberculosis may arise as a cavitary multifocal rapidly fatal complication of pre-existing massive silicosis. In other instances, tuberculosis and silicosis are combined from the outset in the same lesions which initially are proliferative in character, but may terminate in massive irregular excavation or in bronchopneumonic dissemination. Silicosis and tuberculosis also may evolve seemingly independently of one another and in some instances the prognosis remains favorable for protracted periods, cavities rarely occurring and tending to be small when present. Nevertheless, the clinical course ultimately tends to be fatal. Survival is shortest in the first group and seldom exceeds six months. In the second group, an average period of 14 months may elapse between the commencement of the tuberculous spread and death. The third group may continue in reasonable health for years.

Chemotherapy has had but limited effect on the course of tuberculosis in silicosis. Regression of exudative processes and recently disseminated lesions usually are achieved even by the use of streptomycin alone. Cavities with elastic walls, situated in the less heavily silicotic portions of the lungs may be favorably influenced. The best that may be expected when the tuberculous process is far advanced in the presence of severe silicosis, or when the cavitary walls are thick and indurated, is temporary amelioration, even when the drugs are used in combination or in heroic doses. The chief reason for the failure of these antibiotics lies in the extensive concomitant destruction of the pulmonary vasculature. The drugs remain ineffective because they cannot reach the tubercle bacilli, which are imbedded in dominantly ischemic silicotic and tuberculo-silicotic tissues. The impaired circulation is determined not only by morphologic obstructions to blood vessels, but also by angiospasm and the existence of arterio-venous

and broncho-pulmonary vascular anastomoses. Intravenous drug therapy combined with vasodilators deserves trial in these cases.

Pneumothorax or pneumoperitoneum may achieve temporary closure of tuberculous cavities. Even when such lesions have been sealed off apparently by fibrous tissue, a subsequent common infection may cause the cicatrices to disintegrate with recrudescence of the cavitary disease.

Lung surgery has remained of limited value except when the tuberculous process is strictly localized and the silicotic lesions are minimal. Lobectomies and pneumonectomies have been performed successfully for tuberculous complications when the silicotic process was not yet too far advanced. Segmental resection, however, appears to have even more restricted indications.

Effective therapy of silicosis itself has not yet been elaborated and the newer medicaments have found no direct application in this disease. In spite of the powerful anti-inflammatory action of ACTH and corticosteroids, the results of their use in silicosis with some exceptions are discouraging. When clinical amelioration is achieved following their administration, it is generally limited to temporary arrest of associated inflammatory processes. In theory the immature cellular silicotic lesions should be reversible on endocrine therapy, but the disease usually is not recognized clinically until these granulomata have been replaced by fibrous tissue. At this stage, these hormones have no beneficial effect.

The main prophylactic measure against the pneumoconioses remains for the time being engineering control over the sources of noxious dust, fumes and gas exposures. The physician can also make a contribution by early diagnosis of the main process or its complications, combating bronchospasm to obviate emphysema, controlling secondary infections and by judicious psychotherapy to eliminate the likelihood of a neurotic complication of the pulmonary disease.

Case Report Section

Pulmonary Alveolar Microlithiasis Associated with the Inhalation of Snuff in Thailand

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During a routine chest x-ray survey in Bangkok, abnormal pulmonary shadows were encountered in nine men who had been addicted heavily to the inhalation of snuff. These men were accustomed to insufflate powdered snuff into the nose at two or three hour intervals for 20 to 30 years. None had tuberculosis. One of them developed pulmonary symptoms and died showing pulmonary alveolar microlithiasis at autopsy. This disease was described by Friedreich[1] in 1856 and by Puhr[2] in 1933. The morphology and pathogenesis were detailed by Kent, Gilbert, and Meyer[3] in 1955 and they added a case to 14 others in the literature. An additional case was reported the same year by Badger, Gottlieb, and Gaensler.[4]

Case Report—A Thai man, 48 years of age, was discovered in a routine mass chest x-ray survey to have fine mottlings in both lung fields with some sparing of the apices and right middle lobe. Numerous minute calcified specks were visible throughout, with some areas of honey-comb appearance. The heart and diaphragm were almost completely obscured. The trachea was normal in position and size (Figure 1). The antero-posterior diameter of the thorax was shallower than normal. He was asymptomatic except for chronic cough with mucoid sputum for three years and a tendency to catch colds which were accompanied by difficulty of breathing. He had been a snuff addict for 23 years, and took about 7.5 gm. per day in divided doses two to three hours apart. The snuff contained 9.47 per cent calcium. He subsequently was admitted to Nunburi

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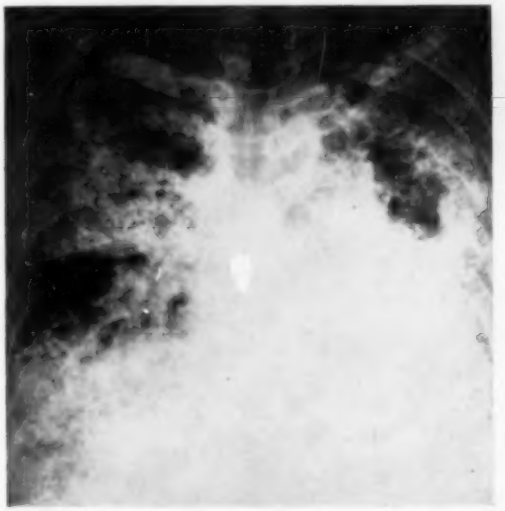

FIGURE 1: Chest x-ray showing extensive mottled densities in both lung fields.

Hospital with symptoms of dyspnea and cyanosis which followed a cold. He soon recovered with penicillin and oxygen, but felt much weaker than before. Examination showed a man of good physical condition. However, he had clubbed fingers, and occasional crepitations were heard over the bases of the lungs. After walking up and down stairs eight meters high, he became tired, his respiratory rate increased, and there was facial cyanosis. Routine laboratory findings were negative except for a moderately positive tuberculin reaction. Histoplasmin, coccidioidin and blastomycin skin tests were negative. Six cultures of sputum revealed no growth of Mycobacteria. The electrocardiogram showed ventricular extra-systole. He died three months later following pneumothorax which attended needle biopsy of the lung.

The autopsy revealed firm red-brown lungs which together weighed 2400 gm. and were sectioned with difficulty. The cut surfaces were coarse and looked like pumice stone. The gritty texture was present throughout. Areas of honey-combing were located subapically in both upper lobes. The pleura was somewhat thickened. A collection of 200 cc. of blood-stained fluid occupied the right thoracic cavity. Analysis showed the dried weight of the lung to be 43.24 per cent (normal about 20 per cent), and the calcium content was 3.96 per cent. The tracheobronchial lymph nodes were enlarged to 2.5 cm., firm, dark brown, and uncalcified. The other organs showed no calcification, nor was there evidence of resorption from the bones.

Microscopically, decalcified sections of the lung showed innumerable intra-alveolar basophilic bodies. These calcific structures were round, laminated, and often completely filled an alveolus. A few were present in pleural lymphatic spaces. The alveolar septa were irregularly thickened and collagenous in patches with obliteration of air spaces (Figure 2). The fibrosis appeared to be secondary to the presence of the calcific bodies. Mononuclear cells and dust cells were noted in some alveoli and interstitial tissue. Occasional small patches of metaplastic osseous tissue replaced a few alveoli and inclosed several of the calcific bodies. The bronchi and larger arteries were not remarkable.

Discussion

The clinical symptoms of the nine patients were limited to history of frequent respiratory infections. Two had dyspnea and tiredness with the exertion of walking or stair-climbing, and they had clubbed fingers. All had negative coccidioidin, histoplasmin, and blastomycin skin tests. At least six samples of sputum from each of those who had positive tuberculin

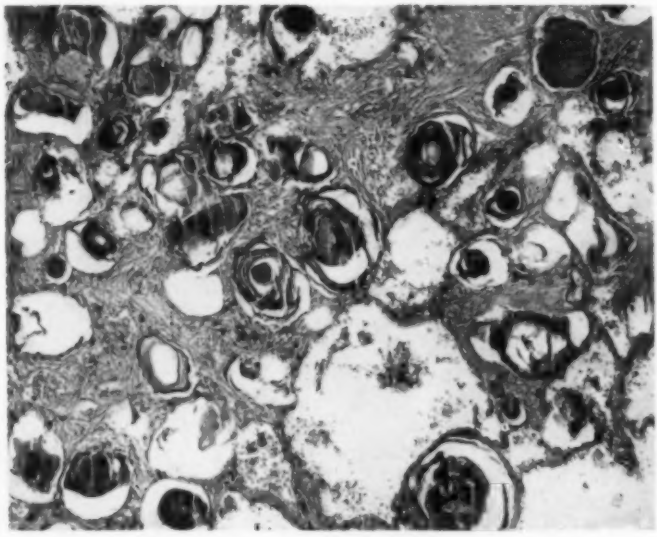

FIGURE 2: Section of lung showing calcific bodies and fibrosis.

tests were cultured for tubercle bacilli with negative results. This experience agrees with the review of clinical findings by Meyer, Gilbert, and Kent,[5] who pointed out that late stages are characterized by respiratory embarrassment, cor pulmonale, and cardiac decompensation. The alterations in the fatal case were classically those of pulmonary microlithiasis.

The snuff used in Thailand is a fine dry tan powder which is taken in small doses with a U-shaped metal tube. One end of the tube is inserted into the nostril and the other end into the mouth. A blast of air from the mouth disperses the powder into the nasal cavity from where it is inspired suddenly, similar to tobacco smoke.

The exact method of preparation of the snuff is secret, but its composition is roughly 50 per cent dry tobacco and 50 per cent oriental gum, with a small part of powdered cuttlebone added. The oriental gum is made by the process of heating "white earth" at high temperature in a kiln. The earth has a high percentage of carbonates and phosphates of calcium. The oriental gum is made into a paste with water and is mixed with tobacco, spread in a thin layer, and allowed to dry in the sun. The mixture is then ground into a powder. Analysis revealed the composition of the commercial powdery snuff to be 75 percent organic material with 15.4 per cent silicates and 1.6 per cent silica.*

The etiology of pulmonary microlithiasis is unknown but is regarded by Kent et al as a "peculiar exudative response to a variety of insults which include pneumonia and rheumatic fever." Four of the patients reviewed by them had been exposed to "dust." Their case was that of a man who worked for five years handling sulfur rocks which were ground and mixed with "some kind of earthy material" requiring the use of a mask because of the high concentration of dust in the air. It would seem possible that the inorganic material in the snuff might have incited a pulmonary exudative reaction leading to microlithiasis. The low content of silica and the nature of the pulmonary lesion excluded silicosis. A filtrate of a suspension of this snuff has been shown to inhibit the activities of the cilia of cells of the palate of frogs. If such a factor operated in the human being, particles of snuff might more easily gain access to the lungs.

In conclusion, a typical case of pulmonary alveolar microlithiasis was associated with inhalation of snuff composed of tobacco and earthy material. The lesion in this case and certain others may have resulted from a hyperimmune reaction to an inhaled irritant as suggested by Kent and associates.

*Analyzed by the Division of Industrial Medicine of the University of Colorado School of Medicine.

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A Case-Study of Perforations of Tuberculous Lymph Nodes into Bronchi and Their Sequelae

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Perforations of caseous tuberculous lymph nodes into bronchi are recognized as a frequent event in primary tuberculosis of childhood,[1] are found increasingly often in the late primary tuberculosis infections of adults,[2,3] and have been described as playing a vital part in the pathogenesis of post-primary tuberculous endogenous re-infections.[4,5]

This case demonstrates the effects of three such perforative lesions in different bronchi of the same lung.

Case Report—The patient was a 24 year old white man who was first treated in a sanatorium for pulmonary tuberculosis five years prior to admission to Warren State Hospital in July 1954.

The tuberculous lesion at the time of initial treatment was confined to the right lung and consisted of spontaneous collapse of the upper lobe with diffuse infiltrations. His sputum contained acid-fast bacilli. Right phrenic crush was performed and pneumoperitoneum was induced.

Eighteen months later a chest radiograph revealed in the right lung "a fairly heavy amount of infiltration in the upper two-thirds, with an area of cavitation extending from the clavicle down to the upper border of the second rib anteriorly—just outside the hilum." His sputum continued to be positive, and he was placed on streptomycin, para-aminosalicylic acid and isoniazid. Pneumoperitoneum was discontinued because an inguinal hernia developed.

Radiographs taken four years after first admission to the sanatorium were reported to show that the cavernous lesion at the level of the first right interspace had become greatly enlarged and its cubic capacity was estimated to have become five or six times its former figure. The lesions were noted to have spread slightly below the cavernous area, but the basal segments of the lung were found to have undergone little, if any change. No lesion was observed in the left lung. The root area, however, appeared more congested and the pulmonary conus enlarged. As his heart was also beginning to deteriorate, it was thought that "he may be developing a cor pulmonale, and if so, would undoubtedly present clinical symptoms of that condition in the not too distant future."

Six months later, on admission to Warren State Hospital for a mental disorder, the pertinent physical findings included cyanosis, marked clubbing of the fingers, and a greatly increased second heart sound in the pulmonary area. There was no evidence of a mediastinal shift, and the chest was symmetrical and appeared to expand equally on both sides. Medium inspiratory rales were heard throughout the entire right lung field, especially in the mid-axillary region, and breath sounds were diminished anteriorly. His sputum was positive and the chest radiographs essentially unchanged.

Ten months after admission he developed gross pitting edema of both legs and bilateral basal rales. In spite of continued intensive treatment his condition steadily deteriorated and he died three months later of cor pulmonale.

Post-mortem examination showed the following relevant findings in the right lung (Figure 1). The upper lobe was found to form no more than an approximately egg-sized, contracted, fibrotic and airless lump. It was separated from the main bronchus of the upper lobe which was mutilated by scar tissue and completely closed at the point of origin of its main subdivisions.

Adhering to the upper lobe remnants were the middle lobe and the apex of the lower lobe. Both the lobes were markedly displaced upwards, and the middle lobe was enlarged to about twice its normal size.

The apex of the lower lobe contained a walnut-sized tuberculous cavity surrounded by fibrotic pulmonary tissue within which few lentil-sized, hard, whitish foci of caseation were clearly visible. The apical bronchus leading directly to the cavity was markedly

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stenotic. In its anterior wall were two narrow fistulae, but the mutilation was most pronounced at the opening of the bronchus into the cavity, where all that remained of an emptied parabronchial lymph node was a small anthracotic mass.

Another typical perforative scar, almost 2 cm. long, was present in the main lower lobe bronchus, only a short distance below the orifice of the apical bronchus. The bronchial wall was somewhat deformed but no parenchymal lesion was detected in the basal segments.

The left lung, also, showed no significant pathological findings.

Comment

Early in the disease, a large complex of tuberculous lymph nodes located in the superior hilum angle perforated into the right upper lobe bronchus, causing destruction of the bronchial wall and distally an aspiration-infiltration of the lung. The resulting collapse of the right upper lobe was observed in the early radiographs although the later progressive contrac-

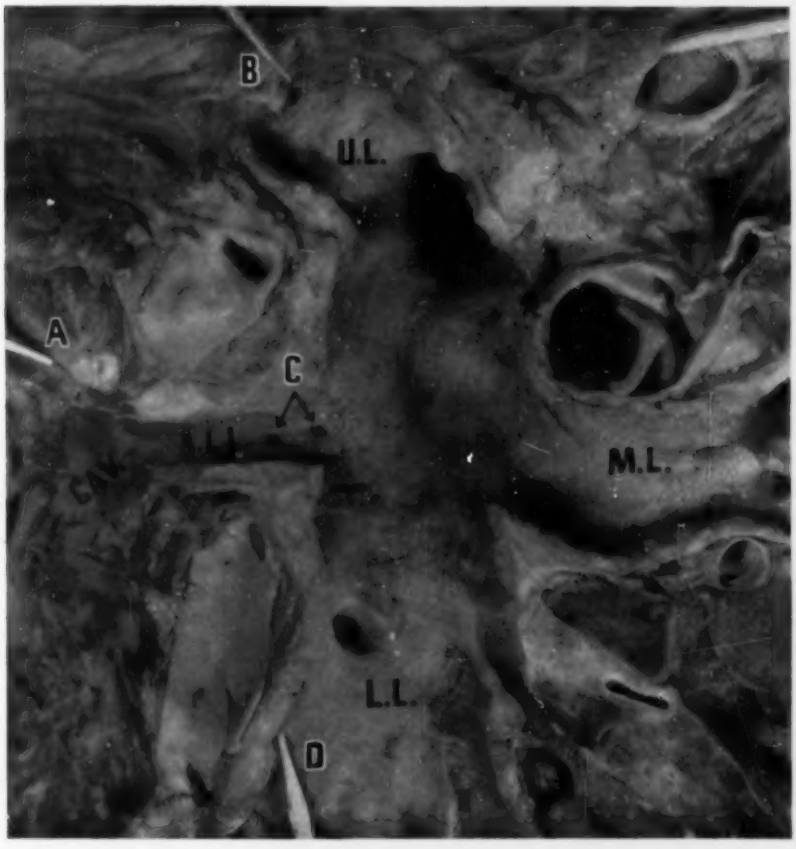

FIGURE 1: Bronchi of the right lung. Note perforative bronchial scars (B) at the site of the amputation of the upper lobe bronchus (U.L.) by tuberculous lymph nodes; perforative tuberculous lymph node fistulae (C) in the apical bronchus of the lower lobe (A.L.L.) and tuberculous cavity (CAV) surrounded by caseous tuberculous foci (A); perforative bronchial scar (D) in the main bronchus of the lower lobe (L.L.).

tion and fibrosis of the infiltrated pulmonary tissue was established neither clinically nor radiologically.

More than a year later, a relapse of the chronic tuberculous process coincided with further perforations of tuberculous lymph nodes, this time into the apical bronchus of the lower lobe. The aspiration-infiltration of the discharged caseous matter into the apical lung segment led to the development of a cavity. The compensatory enlargement of the lower lobe that accompanied the shrinkage of the upper lobe contributed to the increasing distention of the cavity in the second half of the illness.

The age of the scar in the main bronchus of the lower lobe is, in view of the absence of clinical changes at the base, impossible to assess.

Discussion

Tuberculous hilar lymphadenopathies most frequently cause compression of the bronchus of the right upper lobe.[6] Apart from their great density, the lymph nodes of that region often receive lymph flow directly not only from the superior, middle and inferior parts of the right lung, but also from the middle and inferior regions of the left lung.[6, 4]

If compression of the bronchus is severe enough, the upper lobe will collapse. It is then especially vulnerable, since mechanical factors do not act in favor of rapid re-expansion, and the delay may further progressive fibrosis, collapse induration and irreversible shrinkage—changes which probably occur more often than they are diagnosed.

Schwartz[7] described such lesions in a six year old boy who died of tuberculous meningitis. The bean-sized remains of the right upper lobe were wedged in the angle between the trachea and the grossly enlarged middle lobe. This defect was not detected on the routine radiographs.

The radiological appearance of the initial phase of this condition is probably indistinguishable from the so-called "epituberculous infiltration." This is particularly well illustrated by a case reported by Terplan[8] where the chest radiographs of a two year old boy showed "an area of consolidation in the right upper lung and dense infiltration," which, "looked like epituberculous pneumonia." During the following three years his condition steadily improved, and ultimately the radiological shadow of the right upper lung field almost completely disappeared. He died unexpectedly at the age of five from tuberculous meningitis after a long period of excellent health.

The post-mortem examination demonstrated complete occlusion of the right upper lobe bronchus, the lobe itself comprising no more than a fibrotic, cherry-sized lump. The upper tracheo-bronchial lymph nodes were calcified and fused with the wall of the bronchial stump. The middle and lower lobes occupied the entire right pleural cavity. There was no mediastinal shift to the collapsed side, which, Terplan states, can only be expected if the major bronchus leading to the entire lung is occluded.[9]

The introduction of modern chemotherapeutic agents in the treatment of tuberculosis has emphasized the growing importance of tuberculous

lymph nodes. Unlike many tuberculous parenchymatous lesions in the lungs, tuberculous lymph nodes are hardly accessible to the effects of present-day antituberculous drugs, and remain, often for years, a potential threat to the patient. Intercurrent infections, endocrine changes, such as those of puberty, or a lowering of the general resistance of the patient for any reason, might precipitate a reactivation of the disease through the reservoir of tubercle bacilli in the hilar lymph nodes.[10] They then affect the major bronchi through diseased lymphatics and the extracartilagenous mucous glands as described by Reichle and Frost,[11] through a process of penetration-infiltration, and directly through perforation into the lumen.

The recent trend towards this type of dissemination of the disease is seen in the decreasing incidence in the frequency of the classical caseous, ulcerative type of bronchial tuberculosis and the increase in the bronchial wall of more localized processes suggestive of perforative lesions.[12] Of note, in this connection, is a report of occurrences of tuberculous bronchial fistulae during prolonged and intensive treatment with streptomycin and para-aminosalicylic acid.[13]

The perforative lesions often heal without ill effects and the scars that remain blend themselves with the passage of time to the bronchial wall so completely that they can be detected years later only with difficulty. Less frequently they induce a stenosing bronchitis, with disturbances in the ventilation and drainage of the related pulmonary segments, causing atelectasis, bronchiectasis, and the development of fixed stenoses and bronchial strictures of varying degrees of severity.[14] These bronchial stenoses differ from the more diffuse processes that occur in bronchi draining tuberculous cavities or secretory lesions with retention of pus; in the latter, tuberculous lymph nodes may or may not be found in proximity to the affected bronchus and perforative lesions will not be present.

It is, unfortunately, not always possible to determine the pathogenesis of the bronchial lesion in every case, although valuable aids continue to be furnished through advances in the field of radiological and bronchoscopical techniques.[10, 15, 16, 17]

The importance of detecting fresh bronchial perforative lesions as a cause of a recent parenchymatous flare-up lies in the indication for conservative therapy. Treatment aimed at inducing collapse of the affected lobe in these cases risks initiating or furthering the irreversible pathological changes that have been described.

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Allergic Reactions to Dipasic

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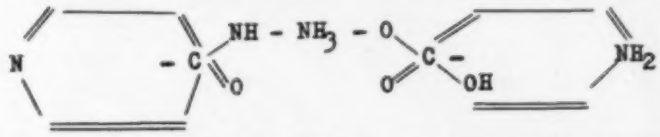
Dipasic,* formerly called GEWO 339, is a para-aminosalicylic (PAS) salt of isonicotinic hydrazine (INH). Its structure is thought to be:



Each Dipasic tablet contains 47.2 mgm. of INH and 52 mgm. of PAS in chemical combination. This substance was first investigated pharmacologically and bacteriologically by Smith and Wiederkehr[1] who found, by *in vitro* testing, that various dilutions of tubercle bacilli, resistant to streptomycin and INH, were sensitive to GEWO 339; and they claimed further that its effectiveness *in vivo* exceeded that of a physical mixture of INH and PAS. In addition, it has been found that, under certain conditions, Dipasic may split to form free PAS and INH.[2, 3]

Aufdermaur and Brodhage[4] found that Dipasic restricted lymphogenous and hematogenous spread of the tubercle bacilli in guinea pigs and that it accelerated the healing process. The latter author[2] suggested that the salt probably possessed a bacteriostatic effect of its own.

The clinical trials of Dipasic in patients with pulmonary tuberculosis showed favorable responses of varying degrees and revealed the presence of no allergic manifestation necessitating cessation of therapy with this d[illegible]g.[4-7]

Of 17 patients included in a bacteriologic and clinical trial of Dipasic, three have experienced allergic responses to Dipasic. The severity of these reactions has required the discontinuance of Dipasic. Because only mild or transient reactions were noted by other workers using Dipasic, it was thought advisable to call attention to these reactions in patients who had such previous sensitivity. Each of the three patients were previously sensitive to para-aminosalicylic acid.

Case 1, No. 3114: W. M., a 72 year old man, was first admitted to Kings County Hospital Medical Center on June 30, 1954 when the diagnosis of bilateral caseopneumonic pulmonary tuberculosis was made on the basis of x-ray manifestations and positive sputa. He was started on streptomycin ½ gm. twice weekly, PAS 4 gm. twice daily, and INH 100 mgm. twice daily, beginning in August 1954. PAS was discontinued because on the ninth of August 1954 he developed erythematous, confluent plaques which were severely pruritic and confined mainly to his trunk. He responded well to the discontinuation of PAS and the administration of chlortrimeton 4 mgm. four times daily. The patient was discharged to the chest clinic in March 1955 on PAS, streptomycin and INH. Another pruritic dermatitis which developed in June 1955 necessitated discontinuing PAS.

From the Department of Medicine, State University of New York, College of Medicine at New York City and The Second Division Pulmonary Disease Service, The Kings County Hospital Center, Brooklyn.

*Dipasic supplied through the courtesy of the Panray Corporation, New York City.

Because of recent positive gastric contents, increased cough and decreased appetite, he was placed on Dipasic 600 mgm. daily on May 11, 1956. After two days of Dipasic he developed generalized pruritus which progressed to a generalized rash with conjunctivitis. By June 22, 1956 these signs and symptoms had all but disappeared after stopping the Dipasic and treatment with benadryl 50 mgm. four times daily.

Case 2, No. 58901: J. L., a 71 year old unemployed man, was admitted to the Second Division Pulmonary Disease Service at Kings County Hospital on the 21st of December, 1955, having been referred by his family physician because of persistently positive sputum and bilateral caseocavitary pulmonary tuberculosis despite some clinical improvement and therapy consisting of INH and daily streptomycin. Ten days after admission he developed generalized pruritus which was not relieved by the mere addition to his regimen of pyribenzamine by mouth, or the intramuscular administration of benadryl.

Eventually all medications had to be stopped because of severe dermatitis which was thought to be due to streptomycin, PAS, and possibly INH. On May 14th, 1956 Dipasic 200 mgm. twice daily was substituted for the previously given anti-tuberculosis drugs. On May 22nd the erythematous, severely pruritic dermatitis recurred and Dipasic was discontinued.

Case 3, No. 14285: C. U., a 48 year old furniture worker, was transferred from the Psychiatric Division on April 5, 1956 with the diagnosis of acute hallucinosis, because of a suspicious-looking x-ray film of the chest. With the history of chronic non-productive cough, 20 pound weight loss, post-tussive rales at the left apex and a chest film showing soft mottling and increased densities throughout both upper lobes, it was felt that there was active pulmonary tuberculosis. Previous examinations by the Board of Health were considered to indicate arrested disease.

On April 12th, he was started on INH and PAS. On May seventh he developed fever, diarrhea and a morbilliform rash over his trunk and extremities. The PAS and INH were discontinued; he received pyribenzamine and by May 14, 1956 his rash and fever had subsided. On this date he was started on Dipasic 200 mgm. twice daily; six hours following his initial dose he experienced nausea, fever, malaise, headache, photophobia, conjunctivitis and had leukocytosis and eosinophilia. The Dipasic was discontinued, he again received pyribenzamine and by May 18, 1956 symptoms had subsided and skin lesions had disappeared.

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Editorial

World Peace

World peace is a subject for medical consideration just as much as is any phase of preventive medicine. The highest ideals of the medical profession have always been for the preservation of mankind. Today the terribly destructive weapons of war threaten the very life of civilization. Therefore, we as physicians should think in terms of how to save man from destruction be it war or disease.

The battle for peace is the battle for life. It is not the battle of one nation but of all nations. It is not a national problem but a world problem. It requires the cooperation of all nations just as truly as does the program for the prevention of pandemic disease.

The conception so commonly held that war is a biological necessity may have been reasonable for one age but certainly it cannot be for this one. Even as late as the beginning of the 2nd World War one important political figure, Bernhardt, put it this way: "War is a biological necessity, a regulative element in the life of mankind which cannot be dispensed with. But it is not only a biological law but a moral obligation and as such an indispensable factor in civilization." By the same kind of reasoning why not advocate the removal of all public health control measures so that death can take its toll and we can call it a biological necessity and a regulative element in the life of mankind.

Our thinking must be elevated above this to save us from destruction and it will be good thinking that will do it. Consider for a moment the abject pessimism displayed by the majority of humans in the days when plagues ran rampant. Most people felt it was a dispensation of a merciful providence and an indispensable factor in civilization. A few thinkers, however, felt differently. They dared to believe that plagues were man made and therefore were vulnerable to human thinking. From this came the control measures for such diseases as diphtheria, typhoid fever, tuberculosis and many others. Of such importance is the thinker. It matters not what field he may represent, nor does it matter from whence the thinker comes. Sound, courageous thinking can come from any part of the world and in any field of human endeavor, be it medicine, law, government, agriculture, engineering or any other field. When we see the pleasant and profitable exchange of scholars and travelers between different countries and the amiable response of neighbor to neighbor we wonder why this is not possible in all walks of life. It is possible if we remember that government was not made to be an instrument of tyrants. It was intended for the protection of people and not their destruction. What does matter in solving this problem is that the thinker dares to believe there is a solution and that past conceptions are not final ones.

In the field of human relationship and understanding it was most encouraging to see at the Fourth International Congress of the American

College of Chest Physicians in Cologne, Germany, the display of free and friendly exchange of ideas that greeted people from all countries. Each country, big or small, willingly contributed its noblest efforts for the benefit for all concerned. It was in true keeping with the highest aspirations in medicine. We give rather than take. If this spirit could but prevail in the domain of international politics—if representatives from each country would have directives from their governments to give for the common good and not take for their selfish interests—then indeed we would be at the gateway of world peace. Civilization would then have taken a great step forward.

It is not improbable that within the framework of the United Nations there will come the final answer to man's longing for peace. This organization founded on the principle of peace among men is indeed the nucleus from which great hopes can be entertained. It needs nourishment, encouragement and courageous thinking from all of us.

In medicine let us continue to promote and encourage the free exchange of thinking and visiting among fellow physicians in every land. Let us not hamper our thinking for world peace by holding to the ancient conception that war is a biological necessity or a regulative element in the life of mankind. It is just as reasonable to conclude that it is good for man to have his head blown off. The highest aspiration of medicine is the preservation of mankind. Let us continue thinking in that direction.

The great need of a change in thinking in government affairs in all nations is in evidence when we realize that certain world leaders still follow the teachings of Machiavelli in the 15th century when he said that a prince ought to direct all his thoughts and faculties in the direction of war for it is the only profession worthy of his pursuit. If that philosophy continues to be upheld in the present bomb age then civilization is indeed doomed. Far better that we recognize the philosophy of Albert Schweitzer—"Reverence for life."

Arnold S. Anderson, M.D., F.C.C.P.*
St. Petersburg, Florida

*Regent, District No. 5.

The President's Page

In December it is customary to review our accomplishments and to make our resolutions for the new year. The College has accomplished many objectives during 1957 and our progress is due entirely to the cooperation and loyalty of our members.

We have seen the formation of three new College chapters during the year: one in Turkey, one in Thailand, and the other in Niteroi, Brazil, making a total of 69 chapters throughout the world. All chapters have been very active, many of them having held two or more meetings in 1957 at which splendid scientific programs were presented. A number of our members in the United States who traveled abroad this year had the opportunity to attend chapter meetings in various countries of the world. The reports received from these members disclosed how highly impressed they were with the outstanding programs presented and the cordial receptions accorded them. One of the objectives of the College is to encourage the interchange of medical information among physicians throughout the world and, indeed, there is no better way than to visit with our colleagues in other countries so that we may know one another better and exchange knowledge and experiences in our specialty.

The largest annual meeting in the history of the College was held in 1957. New York City was host to the 23rd Annual Meeting where registration reached a total of 1884. The scientific program was one of the most diversified and stimulating ever presented by the College reflecting the careful planning and "hard work" of the committee. It is the continued aim of the College to present annual scientific programs of the highest caliber, and because of the zeal with which our program committees have organized this important phase of the College activities, we cannot fail. We are deeply indebted to these devoted members for their cooperation.

This year, 538 chest specialists in all parts of the world were admitted to the College, bringing our total membership to 6,166. Here again the cooperation and interest of our members is evident in the continued growth of the College.

One of the most important phases of the College program is the work of its many councils and committees. New appointments to the councils and committees have recently been completed and their respective projects for the coming year are now under way. I am sure we can expect some very interesting reports at the annual meeting in San Francisco. It is fascinating to review the progress reports of our councils and committees and we are proud to see the interest shown in the final reports published in *Diseases of the Chest*. Here too, we owe a debt of gratitude to the chairmen and members of our councils and committees for their contributions of both time and effort to the College program.

As you are no doubt aware, the College is deeply interested in furthering research in diseases of the chest. Medical science has made great strides in the control of various diseases and research has produced startling discoveries in many fields. We are grateful to munificent contributors who have and are providing the funds to carry on research. The Research and Education Foundation for Chest Disease, which is sponsored by the Council on Research of the College, has a number of approved research projects needing financial support. If you know of some individuals who might be interested in becoming part of a team to give financial support to one or more of these projects, please send their names and full particulars to Mr. Ward Bentley, Executive Secretary, Research and Education Foundation for Chest Disease, 112 East Chestnut Street, Chicago 11, Illinois. Your help is needed in fostering this most worthwhile program.

Our resolution for the year just ahead is to improve and expand in every possible way, the excellent program of the College. I know that we can count on the continued cooperation of every member. To our members and their families throughout the world, my wife and I send Christmas Greetings and good wishes for the New Year.

Burgess L. Gordon

THE HOSPITAL COUNSELOR

The December 1957 issue of *The Hospital Counselor*, a bulletin published by the Council on Hospitals of the College, is now being mailed to our members in the United States and Canada, as well as to other interested physicians. This issue is concerned with the problem of radiation hazards in chest diseases and contains articles by the following physicians:

Benjamin Felson, M.D.
Professor and Director
Department of Radiology
University of Cincinnati
Cincinnati, Ohio

Hymer L. Friedell, M.D.
Professor of Radiology and
Director, Atomic Energy Medical
Research Project
Western Reserve University
Cleveland, Ohio

L. Henry Garland, M.D.
Clinical Professor of Radiology
Stanford University
San Francisco, California

Robert J. Hasterlik, M.D.
Associate Professor of Medicine
University of Chicago, and
Associate Director, Argonne Cancer
Research Hospital, Chicago, Ill.

James E. Perkins, M.D.
Managing Director
National Tuberculosis Association
New York City

Bernard Roswit, M.D.
Associate Clinical Professor
(Radiation Therapy) New York
University-Bellevue Medical Center
Chief, Radiotherapy Service
Veterans Hospital, Bronx, N. Y.

A statement by a General Electric X-ray spokesman, entitled "What has the X-ray Industry been doing about Protection," is also included.

This issue of the Counselor has been prepared under the sponsorship of the Committee on Chest X-ray of the College. Dr. Otto L. Bettag, Chicago, serves as chairman of the Committee on Chest X-ray and has been appointed by the President, Dr. Burgess L. Gordon, as chairman of the Council on Hospitals and Editor of *The Hospital Counselor*, to succeed Dr. Charles A. Brasher, Mount Vernon, Missouri, who asked to be relieved of these duties because of added responsibilities in his position as Medical Director of The State Tuberculosis Sanatorium. Dr. Bettag was formerly chairman of the Committee on Chest Diseases in Institutions, which serves under the Council on Hospitals. Dr. Ernest Teller, Chicago, has been appointed as chairman of the Committee on Chest Diseases in Institutions. Dr. Teller served as vice-chairman of the committee since 1951.

The subject of radiation hazards is currently of great interest and we feel that this issue of *The Hospital Counselor* will be particularly helpful to physicians concerned with the use of radiation therapy and diagnosis. Copies of the December issue of the bulletin may be obtained by writing to the Executive offices of the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

NEWS NOTES

Dr. Aldo A. Luisada, Chicago, Illinois, Director of the Division of Cardiology, Chicago Medical School, was invited by the heart associations of five South American countries to present lectures on cardiology. While on tour, Dr. Luisada spoke before College chapters in Buenos Aires and Rio de Janeiro.

Dr. Thomas S. Fleming, Moberly, Missouri, was recently honored at a banquet given by the Missouri Heart Association. Dr. Fleming was cited for outstanding work in cardiology.

COLLEGE GOVERNOR LECTURES IN SOUTH AMERICA

Dr. Coleman B. Rabin, New York City, Governor of the College for New York State and editor of the forthcoming book, *Roentgenology of the Chest*, sponsored by the College, recently toured South America and spoke before special meetings held by several of our chapters.

In Bogota, Columbia, Dr. Rabin presented two formal lectures and held several clinics which were attended by members of the College.

Upon their arrival in Lima, Peru, Dr. and Mrs. Rabin were met at the airport by Drs. Hector Laos, José Almandos and Carlos López, members of the College. At a special meeting of the Peruvian Chapter, arranged by Professor Ovidio Garvía-Rosell, Regent, and Dr. Victor Narvaes, Chapter President, Dr. Rabin spoke on "The Diagnosis and Management of Diseases with Bronchial Obstructions." The meeting, held at the Hospital Sanatoria No. 1, was well attended and Dr. Rabin's lecture was enthusiastically received. In addition, Dr. Rabin held several clinics in Lima.

Professor Euclydes de Jesus Zerbini, Governor of the College for the State of São Paulo, called a special meeting of the São Paulo Chapter at the University of São Paulo Faculty of Medicine. Members of the College in the São Paulo area as well as many other interested physicians attended this meeting. Following the scientific session, a business meeting of the Chapter was held at which officers for the coming year were elected.

Dr. Rabin spent two weeks in Rio de Janeiro under the auspices of the Instituto Brasil e Estados Unidos, a cultural agency sponsored by the Brazilian and United States Governments. Dr. Mauricio Teichholz, Governor of the College for Rio de Janeiro, arranged a special chapter meeting at the Brazilian Medical Society. Dr. Rabin lectured before an audience of over one hundred College members and guests. Professor Manoel de Abreu, Regent of the College for Brazil, and other College officials, attended the meetings and social functions.

A second lecture was arranged by Dr. Teichholz at the Department of Chest Diseases, under the direction of Professor Aloysio de Paula, at the Policlinica Geral do Rio de Janeiro. Over sixty physicians attended this lecture which was followed by a business meeting of the Rio de Janeiro Chapter where the following officers were elected:

President:	Aloysio de Paula, Rio de Janeiro
Vice-President:	A. Burlamaqui Benchimol, Rio de Janeiro
Secretary-Treasurer:	J. Carvalho Ferreira, Rio de Janeiro

After the business meeting, Dr. and Mrs. Rabin were honor guests at a luncheon given by Dr. Teichholz for the members of the chapter.

During Dr. Rabin's stay in Rio de Janeiro, he was made an Honorary Member of the Brazilian Radiological Society.

Following a brief stop-over in Caracas, Dr. and Mrs. Rabin visited San Juan, Puerto Rico where they were met at the airport by a large delegation of College members and were honor guests at a dinner sponsored by the Chapter. Dr. Jaime F. Pou, Regent of the College, and Dr. José L. Porrata, Secretary of the Puerto Rican Chapter, arranged a meeting of College members at the Puerto Rican Medical Society at which Dr. Rabin lectured. Following this scientific program, Dr. Porrata entertained members of the Chapter at his home.

College Chapter News

STATE OF RIO CHAPTER ORGANIZED

Under the direction of Prof. Dr. Manoel de Abreu, Rio de Janeiro, Brazil, Regent of the College for Brazil, and Dr. Mauricio Teichholz, Rio de Janeiro, Brazil, Governor of the College for Rio de Janeiro, the State of Rio Chapter was officially organized in Niteroi on March 18, with a membership of fifty physicians.

Luncheon held during inaugural meeting of State of Rio Chapter. Lower left: Dr. Mauricio Teichholz, Governor for Rio de Janeiro, Prof. Aloysio de Paula, President, Rio de Janeiro Chapter. Head Table, third from left; Dr. Antonio Jorge Abunahman, Governor for State of Rio Chapter, Prof. Manoel de Abreu, Regent for Brazil, Dr. Nelson Etienne Douat, Vice-President, State of Rio Chapter.

With the approval of the Board of Regents of the College, Dr. Jorge Abunahman of Niteroi was appointed Governor of the College in the Niteroi area, and the following officers for the coming year were elected by the new chapter:

President:	Carlos Antonio da Silva, Niteroi
Vice-President:	Nelson Etienne Douat, Correas/Petropolis
Secretary:	Gil Alves Lima, Niteroi
Treasurer:	Plinio Jotta Cantarino, Niteroi

At the close of the business meeting, a luncheon was given for members of the College. Members of the new chapter are planning meetings to be held next year and have attended several of the meetings recently held by the Rio de Janeiro Chapter.

NEW ENGLAND STATES CHAPTER

The New England States Chapter will present a one-day scientific program on Saturday, January 11 at the Dowling Amphitheatre, Boston, beginning at 9 a.m. The program will consist of three panel discussions and one "stump the experts" x-ray conference.

NEW CHAPTER OFFICERS

KANSAS CHAPTER

President:	Paul H. Wedin, Wichita
Vice-President:	Robert M. Brooker, Topeka
Secretary-Treasurer:	John Fulton, Wichita

MISSISSIPPI CHAPTER

President:	John C. Russell, Cleveland
Vice-President:	Thurman T. Justice, Gulfport
Secretary-Treasurer:	Helen Cannon Bernfield, Jackson

POTOMAC CHAPTER

President:	Roy G. Klepser, Washington, D. C.
Vice-President:	William L. Cook, Charlottesville, West Virginia
Secretary-Treasurer:	Joseph W. Peabody, Jr., Washington, D. C. (re-elected)

VIRGINIA CHAPTER

President:	Edward S. Ray, Richmond
Vice-President:	Samuel M. McDaniel, Norfolk
Secretary-Treasurer:	Charles G. Pearson, Charlottesville

MEXICO CHAPTER

At a meeting held in Mexico City on July 24, Dr. Marvin S. Harris, Los Angeles, spoke before the Mexico Chapter of the College. Dr. Donato G. Alarcon, Mexico City, Regent for the College, also presented a paper at this session. The following chapter officers were elected:

President:	Enrique Staines, Mexico City
Vice-President:	Aradio Lozano Rocha, Mexico City
Secretary-Treasurer:	Fernando Quijano Pittman, Mexico City

NOTICE

The Executive Offices of the American College of Chest Physicians is interested in learning of fathers and sons who are or who have been members of the College. This information is being collected in connection with our 25th Anniversary to be celebrated in 1959. Please send information to the Executive Offices of the College, 112 East Chestnut Street, Chicago 11, Illinois.

Book Reviews

COUGH SYNCOPE, by Vincent J. Derbes, and Andrew Kerr, Jr., M.D. Published by Charles C Thomas, Springfield, Illinois, 1955, 182 pages.

This small volume has all of the characteristics of excellent medical writing. Historical discussion of its topic is given in a fascinating manner portraying the thoroughness and competence of the authors in gathering pertinent information. Inclusion of thirty-six concise case histories serves as an expedient means for conveying relevant data. Ample space is devoted to the differential diagnosis of related conditions. The chapter dealing with theories of the mechanism of cough syncope is rich in minute details and elucidating comments. In other chapters, exposition of the physiologic mechanism as well as the medico-legal aspects of cough syncope reflects critical insight and judicious objectivity.

Because of the noteworthy text, good bibliography and precise artisanship in the production of this book, it is likely to enjoy great popularity with the medical profession.

Andrew L. Banyai, M.D.

SEGMENTAL ANATOMY OF THE LUNGS: A STUDY OF THE PATTERNS OF THE SEGMENTAL BRONCHI AND RELATED VESSELS, by Edward A. Boyden, Ph.D. (Med. Sc.). The Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1955, 276 pages, $15.00.

This volume of 276 pages consists of 10 chapters, contains 124 illustrations, many in color, in addition to 11 full page color plates, a complete bibliography, and an excellent index. It is the result of nine years of intensive work by the author and his colleagues. The need for the information it contains was anticipated by Dr. Owen H. Wangensteen, as it related to the work of his staff in chest surgery. The author points out that after receiving the initial impulse from this surgeon and finding no comprehensive figures of dissection of the mediastinal and interlobar surface of the lungs, he proceeded to make preliminary dissections in order to meet his seminar assignment with Dr. Wangensteen. This taught him that in order to analyze variations in the mode of distribution of bronchi and pulmonary vessels it would be necessary to dissect and inject hundreds of lungs. From such a study the prevailing patterns could be established and then the trends of variation. To facilitate this, the author devised a system of numbering and lettering branches so that corresponding bronchi, arteries, and veins could be given the same number, and thus eliminate many terms. The Jackson-Huber system of naming the segments was employed, but in addition the subsegments were named. The latter are the units that become displaced in the early development of the bronchial tree and thus are essential to an understanding of variations.

Knowledge of segmental anatomy could have little practical value a decade or so before this work was begun, but with the advent of antimicrobial drugs, improved anesthesiology, and liberal use of blood, surgical techniques advanced. However, without the information provided by Boyden and other pioneers in this field, surgical extirpation would probably still be limited to whole lungs and lobes.

In the foreword, Dr. Evarts Graham said, "Everyone with an interest in the subject may congratulate himself that an anatomist of the caliber of Edward Boyden has devoted his energies to the production of this classic work." This is a significant foreword, being written by the surgeon who only in 1933 successfully removed a lung for the first time for malignancy.

Dr. Boyden was already famous for his classical studies on the gall bladder. The work presented in this book on *Segmental Anatomy of the Lungs* is the second contribution to assure him widespread recognition.

Boyden's work not only makes it possible for the surgeon to resect diseased segments with greater accuracy, without sacrificing an entire lobe or a lung, but is also of great value to bronchoscopists, roentgenologists, clinicians, and those who teach anatomy to medical students. This book is packed with important new information which is indispensable to all physicians interested in pulmonary diseases.

J. Arthur Myers, M.D.

FUNDAMENTALS OF CLINICAL FLUOROSCOPY with Essentials of Roentgen Interpretation. Second Edition by Charles B. Storch, M.D. Grune & Stratton Inc. New York, 1956, $8.75.

This compact, comprehensive book embodies the fundamentals of fluoroscopic techniques with the normal and many of the abnormal findings throughout the body. The text, though terse, is detailed and amply clarified by numerous sketches and fluoroscopic reproductions. For each body system the author sets forth in logical sequence his method of fluoroscopy, the normal findings including normal variants, and the salient features of the more common pathological changes. This second edition has been expanded to include sections on congenital heart diseases, small bowel, intestinal obstruction, gallbladder fluoroscopy and neoplastic diseases of the fundus. Many of the pitfalls and limitations of fluoroscopy as well as special techniques of differential diagnosis are described. The illustrations are large and clear; the style is interesting and readable. Dr. Storch has obviously written this book for the student and the practicing physician whether he be a radiologist, internist, or surgeon. For those doctors who employ fluoroscopy as a routine part of their examination, this treatise will serve as an invaluable guide to better diagnosis.

Lloyd K. Mark, M.D.

THE INDEX

TO THIS VOLUME HAS BEEN REMOVED

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Lloyd K. Mark, M.D.

THE EDITORIAL BOARD

FOR

DISEASES OF THE CHEST

is pleased to announce . . .

SECTION ON CARDIOVASCULAR DISEASES

to be published in each issue of the College Journal

DISEASES OF THE CHEST

effective

JANUARY, 1958

This new Section is being established because of the growth of the College and the varied interests of its members. The new Section will facilitate the selection of scientific papers of significance to our readers. The Editorial Board welcomes recommendations at all times relative to the improvement and maintenance of the high standards of the Journal.

J. Arthur Myers, M.D.
Editor-in-Chief

MEDICAL SERVICE BUREAU

POSITIONS AVAILABLE

Board eligible internist wanted for Florida State Tuberculosis Hospitals. Rapidly developing program with opportunities for advancement. Beautiful hospitals. Furnished houses available. Liberal retirement and other benefits. Salary dependent upon qualifications. Write: Roberts Davies, M.D., Director, State Tuberculosis Board, PO Box 286, Tallahassee, Florida.

Asthma. Well-known hospital, expanding pediatric and adult asthma program, seeks internist with special interest in asthma to head service. Such a man would come in on ground floor and help develop complete program involving psychiatric, allergy, and cardio-pulmonary services. Social service, total patient rehabilitation, and research are major elements of program. State salary required. Please address inquiries to Box 294A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Resident physician wanted with chest experience, eligible for New Jersey license. 240-bed general chest disease hospital, with surgical department. Position open February 1, 1958. Maintenance with private apartment available. Communicate with: Medical Director, Passaic County Valley View Hospital, Box 1608, Paterson, New Jersey.

Full-time staff physician wanted for the Idaho State Tuberculosis Hospital, Gooding, Idaho. New, fully modern hospital building recently completed, replacing several small antiquated units. Total bed capacity of 85. Salary governed by training and experience. Apply: Medical Director, Idaho State Tuberculosis Hospital, Gooding, Idaho.

Staff physician wanted for 600-bed, modern tuberculosis hospital. Medical license or eligibility required. Hospital located in college town, 30,000. Active outpatient department. Suspected cases admitted for diagnosis. Vacation, sick leave, retirement and social security. Salary $9360 up, depending on qualifications. Apply: Medical Director, Eastern North Carolina Sanatorium, Wilson, North Carolina.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

24th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 18-22, 1958

Fifth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958

POSTGRADUATE COURSE

11th Annual Postgraduate Course on Diseases of the Chest
Warwick Hotel, Philadelphia, March 3-7, 1958

CHAPTER MEETING

New England States Chapter, Boston, January 11, 1958

ANNOUNCEMENTS

Dr. Charles A. Brasher, Medical Director of the Missouri State Sanatorium, Mount Vernon, announces that the hospital has received approval of the Residency Program in Pulmonary Diseases. This approval has been given by recent action of the Council on Medical Education and Hospitals in concurrence with the Subspecialty Board of Pulmonary Diseases of the American Board of Internal Medicine. The service will be listed in the next Internship and Residency number of the AMA Journal. The sanatorium has previously been approved for a residency program in thoracic surgery.

Improved facilities and better qualified medical staff during the last few years have been responsible for this major step forward and Dr. Brasher states further that these facilities will be available to the University School of Medicine of Missouri and other universities which need an outlet for training which will apply toward the necessary formal training for the Board of Thoracic Surgery or Internal Medicine.

The next postgraduate course in Laryngology and Bronchoesophagology to be given by the University of Illinois College of Medicine is scheduled for the period January 27-February 8, 1958. The course is under the direction of Dr. Paul H. Holinger, Chicago. Information may be obtained from the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

Drs. Chevalier L. Jackson and Charles M. Norris, Philadelphia, have announced that the Department of Laryngology and Bronchoesophagology, Temple University Medical Center, will present the Postgraduate Courses on Bronchoesophagology on the following dates: January 13-24, 1958; March 24-April 4, 1958. Tuition for each course is $250. Further information and applications may be obtained from Dr. Jackson, 3401 North Broad Street, Philadelphia 40, Pennsylvania.

The Chicago Heart Association will sponsor a conference on pulmonary circulation to be held March 20-22, 1958, at the Palmer House in Chicago. The conference will bring together major contributors to this controversial field. Each participant will present his recent work and opportunity will be provided for discussion. The meeting is open to physicians and scientists.

A new synthetic antihistaminic agent, Dimetane, has been introduced recently by the A. H. Robins Company, Inc., of Richmond, Virginia. Dimetane (parabromdylamine Maleate-Robins) provides a high order of antihistaminic effect, high potency resulting in low dosage, high therapeutic index, and low incidence of side effects. It is available in tablets, Extentabs, and elixir.

Romilar CF (Cold Formula), a multiple-action formula for the symptomatic relief of colds and acute upper respiratory disorders, has recently been released by Roche Laboratories, Division of Hoffmann-LaRoche, Inc., Nutley, New Jersey. Romilar CF combines the benefits of Romilar, the non-narcotic cough specific, with an antihistamine, a decongestant, and an analgesic-antipyretic.

The University of Cincinnati Institute of Industrial Health offers graduate fellowships in industrial medicine. The three-year course, leading to the degree Doctor of Science in Industrial Medicine, satisfies the training requirements for certification in Occupational Medicine by the American Board of Preventive Medicine. Two years are devoted to intensive academic and clinical study in the field of industrial medicine. A final year is spent in residency in an industrial medicine department or in some comparable organization. A one-year course is also offered to qualified applicants, with a possibility of a Master of Science Degree. Requests for additional information should be addressed to the Secretary, Institute of Industrial Health, College of Medicine, Eden and Bethesda Avenues, Cincinnati 19, Ohio.

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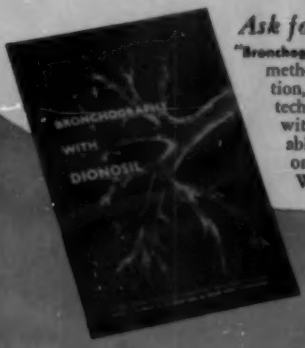

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